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BULLETIN

OF THE NEW YORK ACADEMY OF MEDICINE

Original Articles

by

JOHN P. PETERS

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President's Address, Graduate Fortnight

Section on Microbiology

SECOND SERIES DECEMBER 1949 VOL. 25, NO. 12

BULLETIN OF THE NEW YORK ACADEMY OF MEDICINE

CONTENTS

Advances in Diagnostic Methods 747
Benjamin P. Watson

Diagnostic Significance of Electrolyte Disturbances . . 749
John P. Peters

The Present Status of Clinical Electroencephalography 764
Frederic A. Gibbs

A Chronicle of One Hundred Years of Otolaryngology 775
A. C. Furstenberg

Section on Microbiology:

Chemistry of Chloromycetin, *H. M. Crooks, Jr.* 792

Clinical Use of Synthetic and Fermentation Chloramphenicol (Chloromycetin), *Joseph E. Smadel* 794

Clinical Use of Chloramphenicol (Chloromycetin) in Certain Bacterial Infections, *Theodore E. Woodward* 795

Library Notes:

Recent Accessions to the Library 795

Index, 1949 797

AUTHORS ALONE ARE RESPONSIBLE FOR OPINIONS EXPRESSED IN THEIR CONTRIBUTIONS

MAHLON ASHFORD, *Editor*

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BULLETIN OF
THE NEW YORK ACADEMY
OF MEDICINE

DECEMBER 1949

ADVANCES IN DIAGNOSTIC METHODS

BENJAMIN P. WATSON

President, The New York Academy of Medicine

On behalf of The New York Academy of Medicine I welcome you to this, its Twenty-Second Graduate Fortnight.

The Academy Committee on Medical Education, working through its sub-committees, has always had the responsibility for arranging the programmes. Last year it broke with tradition in selecting "Advances in Therapy" as the general theme in place of, as formerly, submitting a program dealing with diseases related to a particular organ or system. This year the Committee has followed up that break by choosing "Advances in Diagnostic Methods" as a title. This sequence might, in undergraduate teaching, seem to be a little like putting the cart before the horse, but for an informed gathering such as we always have here that is of no consequence.

In the last few years advances in diagnostic methods have been just as notable though perhaps not so sensational and dramatic as those in therapy. To keep pace with those advances in either field requires study and effort on the part of everyone of us, but the effort probably has to

* Opening address, 22nd Graduate Fortnight of The New York Academy of Medicine, October 10, 1949 by the President of the Academy.

be greater in informing ourselves on up-to-date diagnosis, than in applying intelligently the newer therapies.

Even in the days when diagnostic methods were what we regard now as few and crude, the medical student regarded the time spent upon their acquisition as altogether out of proportion to that devoted to treatment. It was only after entering upon the practice of medicine that he realized the importance of these early disciplines in diagnosis.

I can go back to the time when percussion and auscultation were practically the only methods used in the appraisal of cardiac lesions, and the latter practiced through a wooden stethoscope; when there was still debate as to whether blood pressure readings were valid or were of any significance; when a fracture was diagnosed by eliciting crepitus; when the leukocyte count was just beginning to be regarded as of value in the diagnosis of inflammatory lesions; when chemistry was employed only in simple examination of urine or gastric content; when the material obtained by a diagnostic curettage was interpreted as pathological, when in many instances, as we now know, it showed only normal physiological variation.

Glancing over our program for this Fortnight we realize what advances have been made since those days. We now have electrocardiography, cardiac catheterization, angio-cardiography in the diagnosis of diseases of the vascular system; the detailed examination of the blood elements and bone marrow biopsies in blood disorders; renal function tests, liver function tests and liver biopsies; radiologic techniques in the investigation of the gastro-intestinal tract; electro-encephalography in the elucidation of brain pathology; new methods of attacking the problems of bacterial and virus infections and lastly the use of isotopes in throwing light upon all sorts of physiological and pathological states.

The program made up of evening lectures, morning panel discussions and afternoon hospital clinics, is designed to give all of us a general understanding of the advances made in diagnosis in all branches of medicine and at the same time to supply a more detailed and practical exposition to those who are especially interested in particular fields.

I cannot name individually all those who have worked on the planning of this Fortnight or those who are contributing to it, but we should like each of them to know that the Academy is deeply grateful for the time, thought and effort expended.

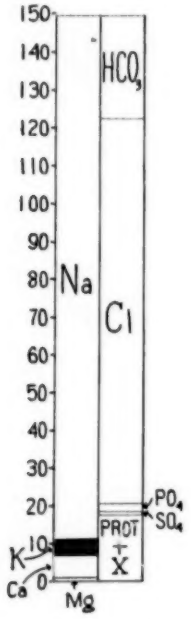
DIAGNOSTIC SIGNIFICANCE OF ELECTROLYTE DISTURBANCES*

JOHN P. PETERS

Professor of Internal Medicine, Yale University School of Medicine

PERHAPS the title chosen for this talk is too broad. Actually, I shall discuss chiefly the sodium salts of blood with brief mention of potassium. If the chemical pattern of normal serum (see Figure 1) is examined, it can be seen at once that 90 per cent of the total electrolyte is composed of sodium salts of which, in turn, more than 90 per cent consists of chloride and bicarbonate. The membranes of the cells of the body are almost impervious to electrolytes, but allow the free passage of water. It follows that the osmotic pressure in all media of the body will be the same and that the distribution of water between the cells and the extracellular fluid will be determined chiefly by the relative concentration of salts in the two media respectively. Since the materials in the cells can only be secured from the extracellular fluid and appear to enter and leave the cells only in connection with metabolic processes, salts of the extracellular fluid, of which serum is a part, play the major role in controlling the distribution of water. Of these, sodium salts are overwhelmingly the most important, not only because of their high concentration, but also because movements of sodium appear to be attuned to the automatic adjustment of exchanges of water. If the concentration of sodium in serum and extracellular fluid (hereafter concentrations in serum only will be mentioned because they mirror precisely concentrations in extracellular fluid, of which serum is a part) rises, the cells will give up water to equalize osmotic pressure. They will, therefore, contract, their contents becoming relatively dehydrated or overconcentrated, while the extracellular fluid will expand proportionally. If the concentration of sodium in the serum falls, the cells will take up water from the extracelluiar fluid. They will, therefore, swell, their contents becoming more diluted. These changes in the concentration of the cellular contents in response to osmotic influences appear to have two

* Given October 11, 1949 before the 22nd Graduate Fortnight of The New York Academy of Medicine.



Na	=	138.0 ± 3.4
K	=	4.1 ± 0.3
Ca	=	5.3 ± 0.3
Mg	=	1.6 ± 0.7
Total Base	=	149.0
HCO_3	=	26.5 ± 1.4
Cl-	=	102.2 ± 2.2
Inorg. P	=	2.0 ± 0.5
SO_4	=	1.4
Protein + undetermined acid	=	17.3
Total Anions	=	149.0

Figure 1—The average concentration and the range of variation of electrolytes in normal serum.

effects: they presumably impair the efficiency of the metabolic processes in the cells; at the same time they provoke reactions in the kidneys and other organs that tend to rectify the disorders of the distribution of fluid. It is conceivable that changes in the concentration of potassium, calcium or magnesium salts could have a similar effect. Changes of the concentrations of these ions large enough to influence osmotic pressure appreciably, however, are not tolerated. A change of only 2 milliequivalents in either direction in the concentration of potassium has serious consequences upon the muscles and heart. Besides, movements of potassium are not linked with the metabolism of water.

For the maintenance of acid-base equilibrium the relative proportions of bicarbonate and chloride and other anions combined with sodium are highly significant; but, for the maintenance of osmotic equilibrium and water exchange, which will be my chief concern, it is the total concentration of sodium salts that counts. Until recently, however,

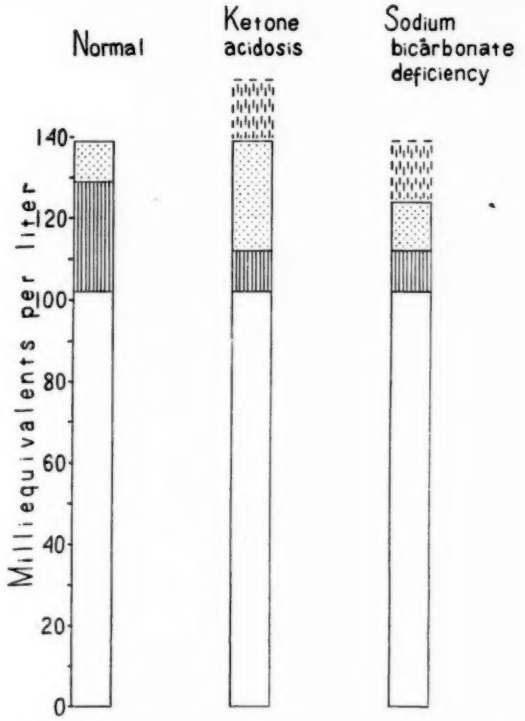


Figure 2—Acidosis from accumulation of acids and from deficiency of sodium. The total height of each column represents the concentration of sodium, the open area represents chloride, the vertically lined area bicarbonate, and the stippled area "undetermined acids." The pattern of average normal serum is shown on the left. The solid outlines in the other columns indicate the patterns of serum in the two types of acidosis. The extensions in broken lines indicate the effect of adding in each case enough sodium bicarbonate to restore the concentration of bicarbonate in the serum to normal.

direct measurement of sodium has had no clinical utility because it has been so difficult and time-consuming. Results of such measurements were of value in retrospect only, as checks on the accuracy of predictions. They could not be used as aids to diagnosis and the conduct of therapy when they were needed because, even with the best management, sodium analyses took 24 hours for completion. For this reason reliance had to be placed upon measurements of chloride—or preferably chloride + bicarbonate—which could be made expeditiously by com-

paratively simple methods. From the figure it is evident that in normal persons the concentration of chloride + bicarbonate is so nearly equal to that of sodium that, if chloride and bicarbonate are known, the concentration of sodium can be established with sufficient accuracy for all clinical purposes. This is not, however, true in a large proportion of disease conditions, because in these disorders other acids accumulate in the blood to displace bicarbonate. Among these we recognize ketone acids in starvation and in diabetes, lactic acid when oxygenation of the tissues is impaired, phosphates and sulfates in severe renal decompensation. The pattern of the serum when such acids accumulate is illustrated in the center of Figure 2, compared with that of average normal serum on the left.

In this and most of the other figures, only the concentrations of sodium, chloride and bicarbonate are given, because these are the only measurable ions that need concern us for the moment. The total height of each column represents sodium, the open area chloride, the vertically lined area bicarbonate, and the stippled area at the top the difference between sodium on the one hand and bicarbonate + chloride on the other. This may be termed the *undetermined acids*. This component, as I said before and as you can see from the figure on the left, in normal persons is quite small. It is also relatively constant. The middle column illustrates the simplest condition encountered in diabetic acidosis, the accumulation in the serum of ketone bodies, β-hydroxybutyric and acetoacetic acid, which have displaced bicarbonate. Under these circumstances it is quite impossible to estimate the concentration of sodium from bicarbonate + chloride without ascertaining the concentration of the undetermined acids, which is not feasible. From the sum of bicarbonate + chloride it would be inferred that sodium was greatly reduced, whereas in point of fact it is quite normal. From the standpoint of therapy it is highly important to ascertain whether or not sodium is depleted. There are two types of acidosis; the one that has just been described and which is depicted in the center of the figure, in which bicarbonate is displaced by a foreign acid; and the one on the right in which there is an actual deficit of sodium. As they have been drawn, the concentrations of bicarbonate + chloride, from which sodium is usually estimated, are identical in the two figures. The condition illustrated on the right constitutes the clearest indication for the administration of sodium bicarbonate because there is a deficiency of

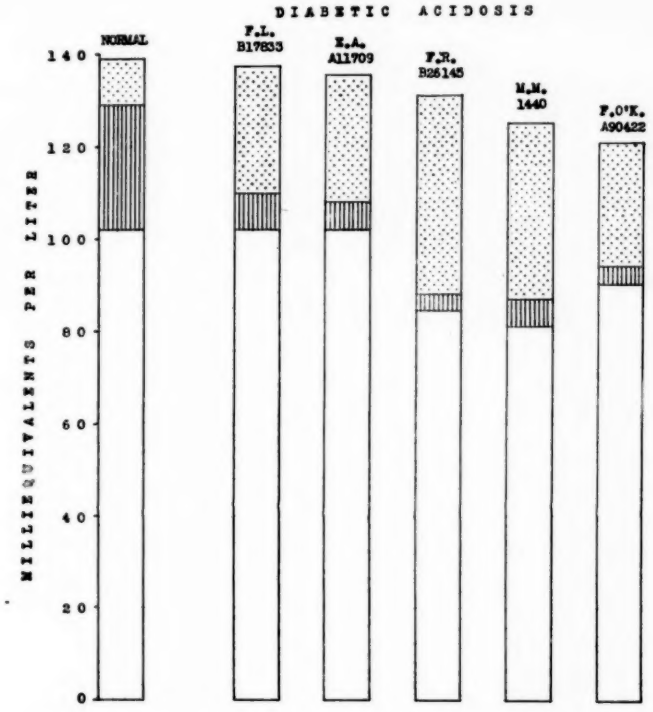


Figure 3—Electrolyte patterns of sera in diabetic acidosis. The total height of each column represents the concentration of sodium, the open portion chloride, the vertically lined portion bicarbonate, the stippled portion "undetermined acids." The pattern of average normal serum is illustrated on the left.

both sodium and bicarbonate. The condition in the center does not. Administration of sodium bicarbonate in this state, though it may restore to normal the concentration of bicarbonate, can do so only by producing an excessive concentration of sodium in the serum, an undesirable disorder. This is shown by the dotted extensions to the columns, which illustrate the effects of adding to each serum sufficient sodium bicarbonate to restore the normal concentration of bicarbonate in the serum. The proper treatment of the condition in the center is to facilitate the utilization and excretion of the abnormal acids which have displaced bicarbonate. In diabetes this can

be effected by giving insulin and carbohydrate together with adequate fluids to inhibit the formation and accelerate the excretion of the ketone bodies. In other states when other acids accumulate in the blood, there may be no such simple solution; but the production of one disorder, sodium excess, to correct another, bicarbonate deficiency, is not a satisfactory escape from the dilemma.

The prediction of sodium from chloride alone, which is done in many clinics, especially surgical clinics, is even more misleading because chloride and bicarbonate can vary independently of one another. This can be illustrated by a series of actual examples from two conditions, diabetic acidosis and lower nephron nephrosis. These have been selected because administration of sodium bicarbonate is so frequently recommended and practiced in these conditions. Figure 3 shows the electrolyte patterns in the serum of a group of patients at the time of admission to the hospital with diabetic acidosis. Again, normal serum is illustrated on the left. All, of course, contain an excess of undetermined acid (in this case, chiefly ketone bodies) and a diminished amount of bicarbonate; but beyond this, all similarity ends. Sodium varies from normal to an extreme deficiency, chloride is often reduced. These variations can be attributed to the relative intensity of various associated disorders: the degree of hyperglycemia and ketosis, diuresis, vomiting and other dehydrating measures, and the quantity of food, fluids and the nature of the treatment the patients have received. Treatment should be directed not toward a hypothetical or ideal diabetic acidosis, according to some stereotyped regime, but to the correction of the particular combination of disorders presented by the patient immediately under consideration. For the proper direction of this treatment the concentrations of sodium, chloride and bicarbonate are all relevant data.

Attention has been called repeatedly to the low bicarbonate concentrations usually found in the sera of patients with anuria or oliguria, particularly in lower nephron nephrosis. The use of sodium bicarbonate —or its equivalent, sodium lactate—is generally advocated for the correction of this disorder. If the serum is properly analyzed in cases with lower nephron nephrosis, it is often discovered that the bicarbonate deficiency is similar to that of diabetic acidosis, not referable to deficiency of sodium, but to accumulation of "undetermined acids." This is illustrated in Figure 4 which shows the course of a patient who developed anuria after a hemolytic transfusion reaction incurred during

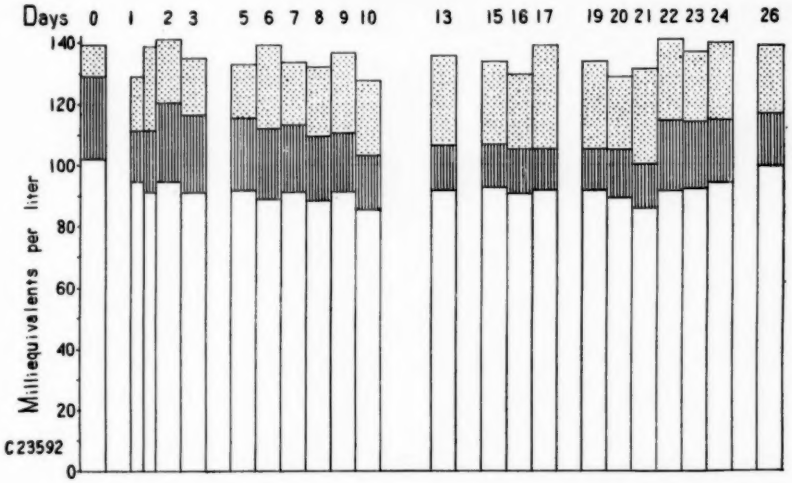


Figure 4—Electrolyte patterns of the serum of a patient during the course of recovery from lower nephron nephrosis.

operation. Again the pattern of normal serum appears at the left. Throughout the period of anuria and recovery illustrated in the figure, bicarbonate is diminished and "undetermined acids" are increased; chloride is also reduced on most occasions. On the other hand, on only two or three occasions, after vomiting, did sodium fall significantly below normal, providing an indication for the administration of bicarbonate. It may be added that the bicarbonate deficiency never attained serious proportions—we hope because of reasonably good management. That such a picture is not consistently found in anuria is shown by Figure 5 which represents electrolyte patterns of sera from a number of cases. These are almost or quite as varied as those of diabetic acidosis. The need for accurate adjustment of the internal environment is, however, far more urgent when no aid can be expected from the kidneys. It is a great comfort, when confronted with such emergencies, to know that it is possible within an hour to learn sugar, nonprotein nitrogen, sodium, potassium, chloride and bicarbonate without exsanguinating the patient. The introduction of the flame photometer, as an adjunct to methods already available, has made this possible.

Deficits of plasma sodium are among the commonest metabolic dis-

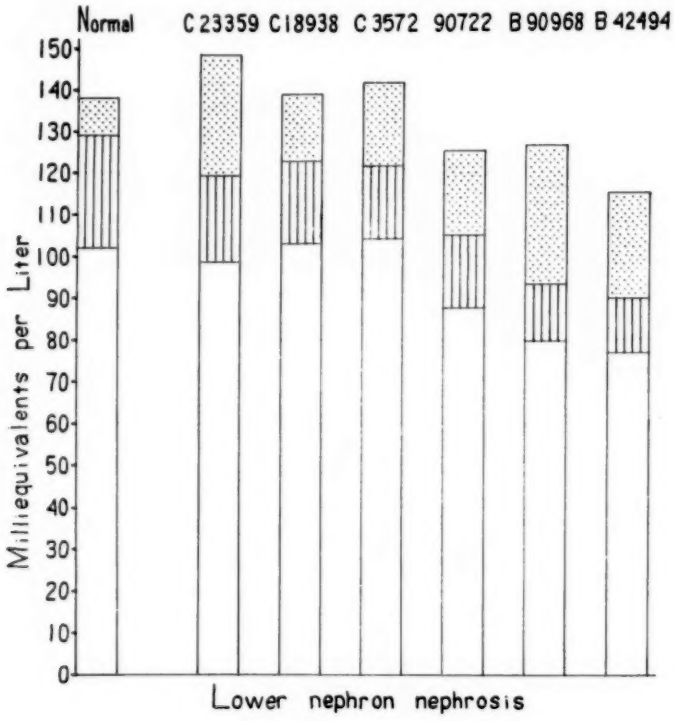


Figure 5—Electrolyte patterns of sera in patients with anuria.

turbances encountered in an active clinic. The reasons for this are several: 1. Sodium is an essential commodity which must be derived from the environment. It is not, however, a natural constituent of vegetable foods and occurs in relatively low concentration in meats and other animal foods. For an adequate supply of sodium reliance is placed on sodium chloride added to food, either in preparation or at the table, or both. When patients are given nutritive liquids or limited diets, care is not always taken to assure an adequate intake of salt. 2. Both sweat and gastrointestinal contents contain sodium. In their excretion of salt the sweat glands are only slightly, the alimentary secretory organs not at all, heedful of the need for or supply of sodium in the body. Profuse sweating, vomiting or diarrhea, therefore, withdraw

sodium salts from the body. Frequently this process is abetted by the unnecessary use of lavage with the aid of various tubes and suction devices by the physician or surgeon. 3. In certain types of disorders the kidneys lose their capacity to protect the salt supplies of the body, which they usually do with the greatest precision. Loss of the ability to reabsorb salt efficiently is one of the characteristics of renal insufficiency, including lower nephron nephrosis. In the presence of this defect sodium chloride and bicarbonate continue to appear in the urine when their concentrations in the serum have fallen far below the normal level. In Addison's disease, also, sodium is wasted through the kidneys. Two other conditions are recognized in which the power of the kidneys to conserve sodium salts is compromised: certain types of intracranial lesions and advanced pulmonary disease, especially tuberculosis. The last is of some importance because, occurring in patients who may be suspected of Addison's diease, it may confuse the diagnosis. There is not time at my disposal to discuss in detail this bizarre disorder to which we have recently devoted much attention. I might say that it should not be confused with the reduction of chloride seen in asthma, emphysema and other conditions in which chloride is depressed by accumulation of CO_2 in the blood. 4. Finally, a certain fear has been engendered in both the lay public and the medical profession of giving salt to sick persons, lest it precipitate circulatory failure.

Sodium deficiency has been defined thus far only in terms of the concentration of sodium salts in the serum and extracellular fluid because it is this concentration that controls the load of water in cells and the responses of the kidney. These organs display no concern about the edema of a thrombophlebitic leg so long as it keeps its place. Though edema may be uncomfortable, unsightly and even embarrassing, it is tolerated by the kidneys so long as it is attended by no disorder of the circulation or the composition of the serum that brings it to the attention of the kidneys. From the standpoint of overall exchanges of salt and of therapy, however, it makes all the difference in the world. The actual amount of sodium in the extracellular fluid is measured by the product of concentration and volume. It is perfectly possible to have a sodium deficit, so far as concentration is concerned, with an excessive amount of sodium in the body, if there is at the same time a greater excess of water. Vice versa, a salt-depleted person may have an abnormally high concentration of sodium in the serum if he is suffi-

ciently dehydrated. It is the incidence and treatment of these two types of states that I particularly want to stress. I shall use for illustration gastrointestinal disorders, reminding you at the same time that profuse sweating or wastage of salt through the kidneys will have an identical effect.

The normal person loses daily about a liter of water without salt by evaporation through the skin and respiratory system. (If, by reason of high environmental or body activity, he sweats, these losses will be much larger and will carry with them salt, but this we shall neglect for the moment.) If the non-sweating individual receives no water in any form, the sodium in his serum will become concentrated because of the loss of insensible perspiration. This is countered at first by the excretion of some salt in the urine. But after a time this stops and the sodium of the serum rises. It seems a paradox that reabsorption of salt should increase when the concentration of sodium in the serum rises; but when there is a deficiency of water this reaction serves a most useful purpose. Every increment of salt in the urine requires for its excretion a certain amount of water. By reabsorbing salt, therefore, the kidneys can save water. But there is a secondary effect that is equally important. As the concentration of sodium in the extracellular fluid rises, the osmotic pressure of that fluid also rises. This causes fluid to be drawn out of the cells. The cells thereby share in the loss of water, protecting the extracellular fluid from extinction. An excessive concentration of sodium in the serum is usually *ipso facto* evidence of dehydration.

The gastrointestinal secretions, with some variations of pattern that may be neglected for our purposes, are isotonic salt solutions, and all fluids introduced into the alimentary canal become isotonic solutions in the process of absorption. If, then, a person receiving no fluids loses by vomiting, diarrhea, fistulae or suction, gastrointestinal secretions or digestive juices, sodium salts and water will be withdrawn in proportional quantities from the extracellular fluid. Of itself this should reduce the volume of fluid in the body without altering the concentration of sodium in that fluid. While this isotonic fluid is withdrawn through the gut, however, the lungs and skin continue to eliminate water alone or hypotonic sweat. Consequently, overall more water than salt is sacrificed and the sodium concentration of the serum rises. Losses of gastrointestinal fluids, if not replaced by any means, cause an accelerated dehydration reaction with elevated serum sodium. Excessive sweating

has the same effect. Confronted with such a picture, the natural reaction is to give only glucose solution in order to lower the concentration of sodium. This is not, however, sufficient. Water or its equivalent may be given to dilute the fluids already in the body, but saline must be given in addition to allow for additional expansion. This subject did lose salt, only he lost proportionally more water. If all the fluid lost is replaced by water—or its parenteral equivalent, glucose solution—this will become at once evident. The concentration of sodium in the serum will fall below normal and the subject will develop stoker's cramps or miner's colic.

In vomiting and diarrhea this picture of dehydration with high sodium is seldom encountered because such patients take or are given water by mouth. Salt is poured into this water by the gut and digestive glands, which are stimulated to secretion by its presence. The consequence is that more salt than water is lost from the body and the concentration of sodium in the serum falls. The proportion of salt lost depends on the amount of water introduced, the length of time it remains in the alimentary canal and the volume that is lost by vomiting or diarrhea or removed by tube. If lavage is practiced, normal saline or slightly hypotonic saline brought to isotonicity with glucose should be used, because such a solution will provoke minimal secretion. It is far better, in the face of intractable vomiting, to give no fluid at all by mouth, relying for the moment on parenteral fluids. If water alone is used, since salt is lost in excess of water in vomitus or lavage fluids, replacement by glucose solution will aggravate the condition grievously. Even normal saline parenterally is inadequate for replacement, because it provides water and salt in equivalent proportions. Attempts to raise the concentration of sodium in the serum by means of normal saline solution will provoke edema with sodium deficiency. In this case the total amount of sodium in the body may be excessive, but its concentration in serum and extracellular fluids is below normal. This causes the cells of the body to become swollen and water-logged. Circulation and renal function fail. This is the condition in which patients with gastrointestinal obstruction or lower nephron nephrosis so often present themselves. The first indication is obviously to arrest the losses of salt by forbidding all oral fluids. It then remains to restore the proper concentration of sodium and the volume of fluid in the body. To achieve this end it has been proposed that all salt be withheld and that only

enough glucose solution be given daily to prevent ketosis and excessive destruction of protein. It is left to the kidneys to make the necessary adjustment by excreting water without salt. Since, however, the necessary amount of glucose—let us say 100 gm.—can not be given without enough water, 1000 cc., to replace that lost by insensible perspiration, this is at best a tedious process. Moreover, until it is completed, circulatory and renal insufficiency will persist. I agree heartily that normal salt solution under such circumstances is contraindicated. Normal saline should be used only to make up the volume of fluid in the body when this is deficient. Normal saline with glucose dissolved in it can also be used to restore the concentration of sodium when the volume of fluid in the body is normal or reduced. In this case insensible perspiration will aid in the adjustment. But to wait on insensible perspiration when there is an excess of fluid in the body seems overcomplacent. The most logical treatment in this condition is the administration intravenously of hypertonic salt solution. A liter of normal saline contains only enough sodium to take care of the liter of water it adds to the body; 300 cc. of 3 per cent sodium chloride, besides providing the salt required for its own volume, contains enough in addition to raise the concentration of 11 additional liters 10 milliequivalents; 500 cc. of a 3 per cent solution will provide 10 milliequivalents for 18 liters; 300 cc. of a 5 per cent solution will do the same for 21 liters. Such solutions, especially the 3 per cent, are well tolerated. Their administration under the circumstances that I have defined does not provoke heart failure and aggravate edema. On the contrary, it is followed by improvement of the circulation and diuresis. What I want to emphasize, however, is the general principle that in the administration of fluids both volume and composition must be evaluated and taken into consideration. Isotonic salt solution and 5 or 10 per cent glucose solution are not the only available instruments for the replacement of body fluids.

It has become increasingly evident that sodium, water and glucose are not the only objects of concern. Disturbances of the concentration of potassium, especially deficiencies of this element, are being reported with increasing frequency. The concentration of potassium in normal serum varies from 3.1 to 5.3 milliequivalents per liter (12 to 20 mg. per cent). If it falls below 2.0 or rises above 7.0 milliequivalents, definite disorders appear. The most serious of these involve the action of the heart and may be detected by means of the electrocardiograph. I shall

not describe these changes now; they have been well defined in the recent literature. It has been suggested that they be used instead of chemical analyses to detect disturbances of serum potassium and as checks on the effects of therapy. Although electrocardiography may be a useful adjunct to chemical analyses for this purpose, it is not an altogether satisfactory substitute. The electrocardiographic disorders, unless they are permitted to run their whole gamut, which is obviously undesirable, are not sufficiently specific to be regarded as pathognomonic. Other symptoms and signs that have been described are even less reliable. Weakness, sometimes approaching paralysis, has been described as a symptom of both hyper- and hypokalemia.

Provided that a person is receiving and absorbing food, a deficiency of potassium is unlikely to develop because potassium is such a ubiquitous component of foods. The subject who is not receiving or absorbing a diet, however, is deprived of this essential element. So long as the function of the kidneys is unimpaired, these organs protect the body most effectively against depletion of sodium, but potassium they conserve with far less efficiency. In the presence of a sodium deficiency, if the kidneys are intact, sodium may be so completely reabsorbed in the tubules of the kidney that only minute traces of the element appear in the urine; a urine free from potassium, on the other hand, has never been described. Potassium exists chiefly in the cells of the body to which it gains access and from which it is discharged, not by a simple process of diffusion, but in connection with metabolic reactions. If, then, potassium leaks from the extracellular fluid into the urine, the cells do not ordinarily replace it completely. In the absence of an exogenous supply of potassium in the form of food, serum potassium does not usually fall to a serious extent because cellular tissue, especially protein, is broken down and with its destruction potassium is released. Gastrointestinal secretions, however, also contain potassium, in concentrations distinctly higher than those found in serum. This element is, therefore, sacrificed in vomitus, diarrhea, fistulae, and when lavage is practiced. This constitutes another contraindication to suction and lavage. There can be no doubt that potassium deficiency of a serious degree has been and is still occurring with great frequency on the surgical services of our hospitals because of failure to recognize these fundamental facts. A very special case of potassium wastage attends the use of desoxycorticosterone. This steroid specifically promotes excretion of potassium.

Patients treated with desoxycorticosterone are, therefore, always in a somewhat precarious state with respect to potassium. So long as they eat and retain their food, they are protected. But, if, because of intercurrent illness or from any other cause, they fail to eat or develop vomiting or diarrhea, their serum potassiums may fall rapidly to dangerous levels.

Excesses of potassium in the serum are less to be feared. The condition in which they are most to be feared are states of extreme renal failure, especially anuria. Even when there is complete anuria, however, serum potassium seldom rises to dangerous concentrations if the composition and volume of the fluids in the body are properly preserved. It is difficult to raise the concentration of potassium in the serum of a normal animal to toxic levels with injections of potassium salts, not only because the potassium is promptly excreted by the kidneys, but also because it is absorbed by the cells. Even if the kidneys are removed, the tolerance for potassium remains quite high because of this protective activity of the cells. If a normal animal is deprived of protein, both nitrogen and potassium are excreted in rather uniform proportions as a result of the destruction of cellular protein. But if an anuric animal is subjected to the same treatment, under proper conditions, nonprotein nitrogen accumulates in the blood serum far more rapidly than potassium does. The potassium is retained in the cells. This power of the cells to take up and retain potassium constitutes an automatic protection against potassium poisoning. Of course there is a limit to this protection and it is not well to tempt nature too far by adding to the endogenous potassium when there is anuria or extreme oliguria. The patient with extreme oliguria or anuria should not receive food containing potassium, which excludes almost all natural nutritive materials. Carbohydrate should, however, be given in sufficient quantities, properly distributed, to maintain continuous carbohydrate combustion. This has a double beneficial effect. It minimizes the destruction of protein and promotes the retention of potassium by the cells, because the segregation of potassium in cells seems to be linked with utilization of carbohydrate.

This is most vividly illustrated in diabetic acidosis. At the height of this condition, when carbohydrate combustion is reduced to a minimum and renal function, owing to dehydration and circulatory collapse, is greatly impaired, potassium in the serum is usually elevated, sometimes to dangerous concentrations. When combustion of carbohydrate is

restored by insulin and glucose, and renal function repaired by administration of fluid and salt, serum potassium falls rapidly, sometimes to equally dangerous concentrations. This drop is the result of three processes: excretion by the kidneys, dilution by expansion of the body fluids, and movement into the cells under the impulse of the resumption of carbohydrate combustion. If, at this time, the patient can and does take food and fluids by mouth, these will provide protective quantities of potassium. If he can not, potassium must be given. It is, however, essential to know whether potassium has fallen before administering it. It would be a fatal error to give potassium in the early stage while its concentration in the serum is still elevated. Potassium chloride or a neutral solution of potassium phosphate may be given slowly intravenously. For this purpose it is our custom to dissolve about 100 milliequivalents of potassium (7.5 gm. of potassium chloride) in 500 cc. of distilled water. This can be diluted with from 500 cc. to a liter of normal saline or glucose solution. It may be necessary to repeat this dose.

It is evident from what has been said that, although the proper sphere of action of potassium is within the cells, where it must serve specific functions, effects of either deficiency or excess become apparent only when its concentration in the serum and extracellular fluids is altered. The load of potassium in cells can be varied within wide limits without recognizable response, so long as its concentration in the serum is normal. The most striking illustration of this is the syndrome of familial periodic paralysis. During the paralytic attacks, potassium is transferred, presumably by reason of some metabolic disorder, from the extracellular fluid into the cells, causing serum potassium to fall. If extra potassium is given, it may be taken up by the cells in the same way. There is, therefore, an overload of potassium in the cells. Nevertheless, the reactions of the patient, including electrocardiographic changes, are those characteristic of potassium deficiency.

This has been no organized analysis of electrolyte and water metabolism; but a rather hurried sketch of certain types of disturbances. My purpose has been to show that modern diagnosis and therapy by the aid of chemistry require more careful analysis of clinical disorders and more carefully considered individualized treatment. Knowledge and technical aids are available; it is time they were more widely and wisely utilized in the clinic.

THE PRESENT STATUS OF CLINICAL ELECTROENCEPHALOGRAPHY*

FREDERIC A. GIBBS

University of Illinois College of Medicine
Department of Psychiatry, Illinois Neuropsychiatric Institute, Chicago

THE clinical investigator has found in electroencephalography a powerful tool with which to attack some of the most baffling of the problems of nervous and mental disease. It is the purpose of the present report to summarize certain recent advances and to indicate what use can now be made of the electroencephalogram in practical clinical studies.

Before proceeding to this task, honor should be paid to those who pioneered. It was, of course, Hans Berger who pointed the way.[1] He showed that the electroencephalogram is surprisingly easy to record, but more importantly that it changes with age, with attention and with states of impaired consciousness. Credit should go to Fischer[2] who showed that abnormal cortical potentials appear during convulsions, and to Tönnies who demonstrated the practicability of ink-writing electroencephalographs,[3] and to Albert Grass, who provided superb equipment for electroencephalographers throughout the world.[4] The contributions of Kornmüller,[5] Grey Walter,[6] Adrian,[7] Bremer,[8] Jasper[9] and others[10] gave basic information and orientation to all early investigators.

In the past 30 years practically every normal and abnormal state of central nervous function in man and animals has been surveyed electroencephalographically. Tens of thousands of men, women and children have been studied with multi-channel equipment. Thousands of miles of records have been inspected and correlated with various clinical conditions. This work has placed electroencephalographic diagnosis on a solid statistical basis, but it has done more than that; it has made the electroencephalographer familiar with his instrument and his material so that he can look through the electroencephalogram at the

* Presented October 20, 1949 before the 22nd Graduate Fortnight of The New York Academy of Medicine.

brain.* In this respect he is like the roentgenologist who looks not at the grains of emulsion on the X-ray film, but at the picture of body structures. The electroencephalographer sees the 400 feet of paper with six or eight wiggly lines on it that forms the electroencephalogram, not in terms of its primary aspects but in terms of its neurophysiological and clinical correlates. Five sets of data have shown important correlations with the electroencephalogram: 1) brain metabolism; 2) age; 3) the level of consciousness; 4) the clinical symptomatology of epilepsy and related brain disorder (trauma, encephalitis, vascular disease, etc.); 5) the pharmacological action of stimulants, sedative and anti-epileptic substances.

The electroencephalogram gives evidence of a type of activity which must be described in general terms because, though it is found more highly developed in nerve cells than in the other tissues, it is nevertheless characteristic of protoplasm in general. It has been termed irritability; the tendency to release stored energy after thermal, chemical, mechanical or electrical stimulation. Voltage production is one form of energy release.

A tendency to rhythmic electrical activity is inherent in all neurone aggregates (ganglia, cord and brain). The cortex shows electrical pulsations with a voltage of approximately 5-500 microvolts and a frequency of 1-50 cycles per second. The primary sources of energy for the fluctuating voltage are glucose and oxygen. To use a mechanical analogy, these two substances are the mainspring of the oscillator, but the escapement or control of energy release lies elsewhere: in CO_2 tension[11] and in as yet unknown enzymes and neuronal mechanisms. Obviously any tissue which has as a major characteristic the release of energy must be provided also with mechanisms for storing energy and regulating its release. Although these mechanisms are not yet understood their operation is manifest in the electroencephalogram, for here one sees energy (derived primarily from the blood stream) transferred to the nervous

* Persons professionally interested in electroencephalography are now organized in many countries. The names, secretaries, and number of members of some of these societies are as follows:

English—The Electroencephalographic Society, Great Britain, W. Grey Walter, M.D., Secretary, Burden Neurological Institute, Bristol, England. 72 members.

French—Société D'EEG et des Sciences Connexes de Langue Française, Henri Gastaut, M.D., Secretary, 149 Promenade de la Corniche, Marseille, France. 50 members.

Italian—Italian Electroencephalographic Society, G. Moruzzi, M.D., Secretary, University of Pisa, Pisa, Italy. 30 members.

American—American Electroencephalographic Society, Dr. Robert Schwab, Secretary, Massachusetts General Hospital, Boston 14, Massachusetts. 107 members.

These societies have united to publish "Electroencephalography and Clinical Neurophysiology, an International Journal." Dr. Herbert Jasper, Neurological Institute, Montreal, Canada, is Editor-in-Chief.

system in finely graded quantities and channeled through neuronal pathways in a precisely regulated manner. This regulation of energy release is of extreme importance for proper function. Modulation or control of energy release in the nervous system is of two types: In the nerve fibers where conduction is the primary function, amplitude is held relatively constant and frequency is modulated (as is conventional in radio communication whenever interference must be kept to a minimum), but in synaptic areas (near the cell body) where interference, interaction and mixing are essential to normal function, amplitude modulation is combined with frequency modulation.

If more than the usual amount of energy is released, as evidenced by increased voltage production per unit time, clinical signs of hyperactivity appear. If less than the usual amount of energy is released, as evidenced by a decrease in the voltage production per unit time, clinical signs of depression of neuronal function appear. The specific symptoms that develop depend on the function subserved by the structures involved in the abnormal energy release. Thus it can be said that the general character of the dysfunction (hyper or hypo) and its time course are electro-chemically determined, but the specific symptom is anatomically determined.

Electroencephalographic patterns have their simplest form and the electrical sign (negativity or positivity) is most easily interpreted when voltage readings from points on the scalp (or some part of the brain) are referred to a relatively inactive reference point (usually the ear lobe). This has been called "monopolar recording." The term is inappropriate, however, because recording with one electrode is impossible. The term "bi-polar" has been applied to recordings from serial pairs of electrodes arranged in the form of a triangle or a line, the activity of each pair being referred back or forward to the next pair. The final description of voltage conditions in the brain will be the same whether activity is recorded with a common reference or with a series of references.

When the electrical activity of the brain is recorded between two electrodes A and B on the head, the possibility arises that both are active and that the resultant tracing is the algebraic sum of the two activities. "Bi-polar" recording tries to subtract from the sum of the activity at A and B other sums obtained by using A and B in conjunction with other points, thus arriving at an evaluation of the voltage con-

ditions at A and B. When a common reference is used the "stigmatic" electrodes are placed at A and B and any difference between the activity recorded is attributable to differences in voltage at A and B, the points in question; thus also for activity recorded from all other points to the common reference. In some cases, however, universal activity may be registered which may be due to activity at the reference point. This may be checked by moving to another reference. However, the same difficulty may arise with the new reference. By removing the reference point further away from the presumed voltage source, shunting is obtained which will tend to reduce the pick-up of activity. For most purposes the ear lobes are sufficiently removed from the brain to serve as satisfactory reference points. However, the anterior temporal spike focus of psychomotor epilepsy, which will be discussed later, usually spreads to the ear, and slow activity is also commonly recorded from the ear in cases with a tumor of the temporal lobe. The opposite ear may be used as reference in such cases or the vertex or occipital region may provide a satisfactory "quiet" reference, or recourse may be had to electrodes on the nose or on the chin. In order to get well away from the brain it may be desirable to place electrodes on the chest and use these as a reference.[12] The complication introduced by the electocardiogram can be avoided if electrodes are placed symmetrically on opposite sides of the heart and interconnected through a potentiometer. Rather than pick up the full voltage of the heart it is desirable to keep somewhat away from it, and the positions ordinarily chosen for chest electrodes are the spine of the first thoracic vertebra and the right sterno-clavicular junction.

From animal experiments[13] and from recordings in the depths of the human brain[14] a negative voltage (referred to a relatively inactive reference) indicates that the electrode is in or on the discharging area. A positive discharge indicates that the electrode is beyond the discharging area.

Excessive thermal, mechanical, chemical or electrical stimulation slows, decreases and finally abolishes cortical voltage production.[15] Thus, flattening of the electroencephalogram and disappearance of the brain waves can be considered an extreme form of slowing.* Depression

* A decrease in amplitude to the point of flattening is rarely encountered clinically. It is an extreme change which carries with it an immediate danger of death. A depression of amplitude resulting in an asymmetry of voltage production from homologous areas in the two hemispheres is a sign of minimal damage and has some clinical localizing value.

of voltage production (slowing or flattening) is a *primary* reaction to injury. In some cases, after mild depression of voltage production or during the phase of recovery from severe depression, a secondary disturbance develops; it consists of paroxysmal *excessive* voltage production. As indicated by the sudden failure of cortical function when the blood supply is cut off, the normal energy consumption of the brain is almost identical with the rate at which it is supplied. Therefore, abnormally great release of energy in the cortex is quickly limited by failure of energy supplies and followed by diminution or absence of voltage production. Excessive voltage production tends to spread, however, and to drive neighboring and connected neurones into similar activity. The greater the excess of voltage the greater the spread and the less precisely the voltage is held within the usual neuronal channels. This reaction of paroxysmal excessive voltage production is an irritative reaction to injury; it constitutes the pathological, physiological basis of epilepsy.

From the electroencephalographic point of view, epilepsy is a disorder of rate regulation which manifests itself as a tendency to abnormally violent and extensive discharge, i.e., as a failure to provide proper spacial and temporal limitation of voltage production. This failure of rate regulation is produced by the same agents which produce normal alterations of rate regulation, mechanical, thermal, electrical or chemical stimulation, but these must surpass certain physiological limits of intensity and duration. Epilepsy can be considered a "tumor of function;" a distortion of one of the chief normal functions of neurone aggregates (i.e., voltage production). Just as a true tumor can be considered a disturbance of temporal and spacial regulation of the rate of reproduction (a feebly represented function in neurones) so an epileptic seizure can be regarded as a failure of the temporal and spacial regulation of energy release. In this view epilepsy is not a disease, but a type of dysfunction. It can have no single etiology and will have as varied a symptomatology as the nervous system has specific receptor, effector and integrator functions. It will certainly be caused by many types of injury and almost any type of injury will be found in some cases to be imitated by a genetic defect.

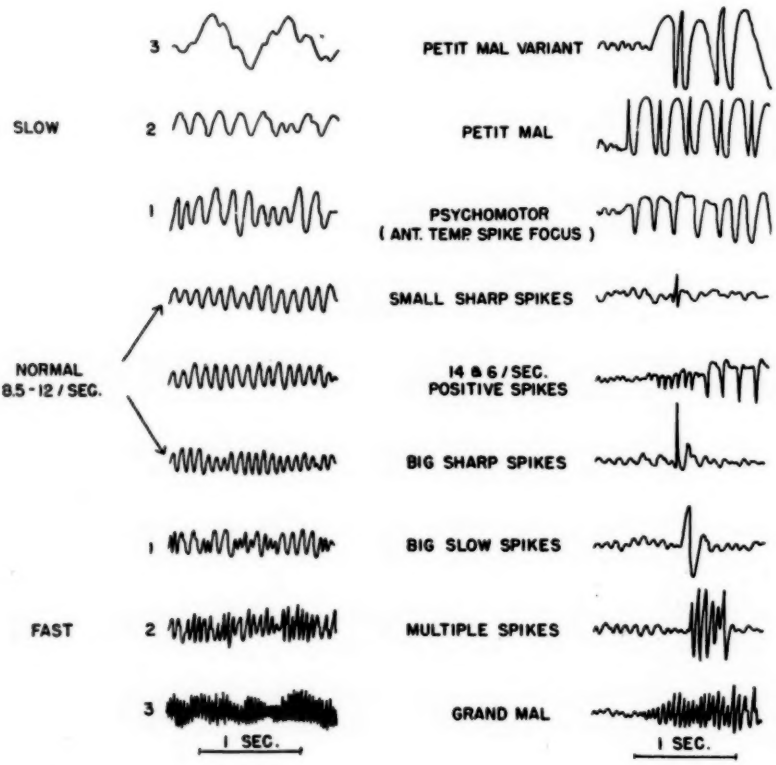
In epilepsy three general types of abnormal voltage production are encountered. They are referred to as seizure patterns.[16] The first is a discharge of unusually fast waves of increasing amplitude followed by interrupted fast waves and later by slow activity. This is the classical

tonic-clonic or grand mal type of seizure discharge (Fig. 1). If the entire brain is involved maximal neuronal activity becomes manifest in generalized muscular contractions and complete loss of consciousness. From the point of view of energy consumption it represents a supermaximal discharge which cuts deeply into the energy reserves and requires a relatively long period of recovery (stupor) before normal voltage production returns. The second type of discharge is the spike-and-wave pattern which appears in its most perfect form as the three-per-second wave-and-spike of petit mal epilepsy (Fig. 1). In this type of discharge each spike of excessive voltage production is followed by a third-of-a-second of stupor (the slow wave) which apparently allows for recovery of function and the possibility of another discharge. However, as the pattern continues the spike usually tends to drop in voltage and the frequency of the repetitive pattern tends to slow from an initial approximately four-per-second to a final two-per-second rhythm. This type of discharge is rarely followed by stupor; it is a relatively conservative paroxysmal dysrhythmia, and is less disorganizing to central nervous function than the grand mal type of discharge. It is associated with three-per-second clonic movements of the head and eyes, posture is usually maintained, and consciousness is commonly diminished but not completely lost. The third type of seizure pattern consists of high-voltage six-per-second and square or saw-toothed four-per-second waves. This type of discharge is referred to as a psychomotor discharge (Fig. 1). It is associated with mental confusion and poorly coördinated but apparently purposeful movements. It is rarely followed by stupor. The psychomotor pattern is the one which is the most nearly normal of the three chief types of seizure discharge. Further study has shown that it is associated with a focus of negative single spike-seizure activity in the anterior temporal region.[17]

A single spike (Fig. 1) is the minimal epileptic discharge; it is commonly asymptomatic, and commonly focal. Spike foci can occur anywhere in the cortex, but they are particularly common in the anterior temporal region. A spike focus in the anterior temporal region has been called a psychomotor type of focus because it is usually associated with psychomotor seizures (trance-like attacks and confusional episodes). The extreme commonness of a focus of spike-seizure activity in the anterior temporal region suggests that this is the most vulnerable of all cortical areas to the irritative type of injury which underlies epilepsy.[18]

FIGURE I

TYPES OF NORMAL AND ABNORMAL ELECTROENCEPHALOGRAM



In the left column are shown the non-paroxysmal patterns; above are those that are abnormally slow for adults, and below, those that are abnormally fast. In the middle are patterns which fall in the 8½ to 12 per second range which is normal for adults. The scale of abnormality reads from one to three, with one being slightly abnormal; two, very abnormal, and three, exceedingly abnormal. This scale, however, must be adjusted for age. The paroxysmal patterns shown in the righthand column are given descriptive names or are named after the clinical type of seizure with which they are most commonly associated. The pattern referred to as "psychomotor" appears as a generalized disorder over the entire cortex during a clinical seizure of the psychomotor type. In seizure-free intervals, particularly during sleep, the psychomotor disorder appears as a focus of negative spike seizure potentials in the anterior temporal region. The 14 and 6 per second positive spikes are in reality two patterns which can appear independently as 14 or 6 per second positive spikes.

It is not enough to determine that the electroencephalogram shows seizure discharges or epileptic waves. The type of wave is important for diagnosis and prognosis. Seizure discharges of the grand mal type are benefited by Dilantin,* phenobarbital and Mesantoin,* whereas the three-per-second spike-and-wave of petit mal responds to Tridione* and Paradione.* Seizures of the psychomotor type are commonly resistant to medication.

In the waking state, with electrodes fastened to the scalp, the activity of the underlying cortex is recorded. During sleep deeper centers take over the regulation of cortical activity. Voltage production in sleep is generally conservative. i.e., slower than the normal waking activity, but with deeper sleep slower and slower potentials appear.[19] The patterns at different levels of sleep are so different that it seems reasonable to suppose that the pacemaking drive or control of cortical frequency is progressively shifted to slower and *lower* centers. Sleep projects some types of subcortical disorder onto the cortex where they can be seen by the electroencephalographer with surface electrodes.[20] It potentiates all types of seizure activity; it largely eliminates age difference; it makes possible recordings on uncoöperative patients. It more than doubles the total clinical value of electroencephalography.

Over 50 per cent of patients with psychomotor epilepsy (i.e., confusional episodes and an anterior temporal spike focus) have personality disorders;[18] in half of these the personality disturbance is so severe that it can be classified as a psychosis. The psychiatric disorder is independent of the epileptic component; it is likely to become intensified when the psychomotor seizures are controlled with medication.[22] Anterior temporal lobectomy, which has been tried by Dr. Percival Bailey, has resulted in improvement of both the psychiatric and epileptic disorders in some cases.[23] The anatomical structures involved in the epileptic and psychiatric symptomatology of psychomotor epilepsy are the same, but the physiological basis of these two components are antithetic. This is probably the same antithesis which is employed for therapeutic purposes in convulsive shock therapy.

Another type of paroxysmal discharge consists of 14 and 6 per second positive spikes which appear in light sleep.[24] It is believed that because of the positive electrical sign of these discharges they come from

* These are trade names for 5,5 diphenylhydantoin; 3 methyl 5, 5-phenylethyl hydantoin; 3,5,5-trimethyloxazolidine 2,4-dione; and 3,5-dimethyl-5 ethyloxazolidine 2,4-dione.

the depths of the brain. The frequency of 14 and 6 per second suggests that they arise in the thalamus where potentials of this general frequency have been localized by Morison et al[25] in the general region of the internal medullary lamina. Such discharges are usually associated with a history of "fainting spells" and a variety of symptoms suggesting thalamic disturbances.

A report in preparation[26] will deal in detail with exceedingly fast non-paroxysmal activity (35-40 per second) (Fig. 1, F-3) which appears best in the precentral regions during light sleep. This, like very fast activity (Fig. 1, F-2), correlates with epilepsy and related organic brain disorder, but it is commonly associated with personality disturbances and is particularly common in post-traumatic psychosis.

By regarding focal evidence of primary and secondary reactions to injury the informed electroencephalographer with adequate equipment is able in many instances to localize lesions which are not apparent from neurologic or roentgenographic examination. Thus, the modern neurosurgeon or neurologist finds the electroencephalograph indispensable. He will not be surprised or too disappointed by cases in which a huge atrophy or widespread demyelination shows little or nothing in the electroencephalogram, for destruction of neural elements does not show well in the electroencephalogram; absence of activity is by no means as evident as disordered activity. An inflammatory process, like acute encephalitis, tends to give maximal electroencephalographic findings even in cases where there are minimal clinical signs, and this helps to distinguish it from a more chronic disorder, for example, multiple sclerosis where the electroencephalographic findings are usually slight compared with the clinical signs. Likewise, a small metastatic carcinoma in the cerebral cortex, because of its rapid growth, usually produces more electroencephalographic disorder than a huge but slow-growing meningioma. If electroencephalography is to be used successfully by the clinician he must familiarize himself with it and realize that the electroencephalograph shows functional rather than structural disorder. The severest electroencephalographic disturbances, for example, convulsions and stupor, are not usually associated with demonstrable structural change. A violently discharging epileptic focus, when identified at operation by direct recording from the cortex, and when ablated by the neurosurgeon, commonly appears normal to microscopic examination.[27]

Although electroencephalography is of value as a supplementary aid

to classical neurology and neurosurgery, which subjects deal with gross or microscopic evidence of structural changes (pathological anatomy), it does something more, something new. Although it does not correlate well with anatomical changes and signs of structural deficits which are essentially irreversible, it does correlate with pathological-physiologic changes which are reversible and amenable to medical and surgical therapy. It opens a new field of dynamic neurology and physiological psychiatry. Hans Berger would be happy to see how his brain child has prospered.

REFERENCES

1. Berger, H. Ueber das Elektrenkephalogramm des Menschen, *Arch. f. Psychiat.*, 1929, *87*:527.
2. Fischer, M. H. and Löwenbach, H. Aktionsströme des Zentralnervensystems unter der Einwirkung von Krampfgiften: Strychnin und Pikrotoxin, *Arch. f. exper. Path. u. Pharmakol.*, 1934, *174*: 357.
3. Tönnies, J. F. Der Neurograph, ein Apparat zur unmittelbar sichtbaren Registrierung biolektrischer Erscheinungen, *Deutsche Ztschr. f. Nervenh.*, 1933, *130*: 60.
4. Grass, A. M. *Instruction manual for the Grass electroencephalograph.* Quincy, Mass., November 1943-49.
5. Kornmüller, A. E. Architektonische Lokalisation bioelektrischer Erscheinungen auf der Grosshirnrinde; Untersuchungen am Kaninchen bei Augenbelichtung, *J. f. Psychol. u. Neurol.*, 1932, *44*:447.
6. Walter, W. G. The location of cerebral tumours by electroencephalography, *Lancet*, 1936, *2*:305.
7. Adrian, E. D. Electrical activity of the nervous system, *Arch. Neurol. & Psychiat.*, 1934, *32*:1125.
8. Bremer, F. Cerveau "isolé" et physiologie du sommeil, *Compt. rend. Soc. de biol.*, 1935, *118*:1235.
9. Jasper, H. H. and Carmichael, L. Electrical potentials from the intact human brain, *Science*, 1935, *81*:51.
10. Gibbs, F. A., Davis, H. and Lennox, W. G. The electroencephalogram in epilepsy and in conditions of impaired consciousness, *Arch. Neurol. & Psychiat.*, 1935, *34*:1133.
11. Lennox, W. G., Gibbs, F. A. and Gibbs, E. L. The relationship in man of cerebral activity to blood flow and to blood constituents, *J. Neurol. & Psychiat.*, 1938, *1*:211.
12. Gibbs, F. A. and Stevenson, W. Noncephalic common reference electrodes, reported at the Central Association of Electroencephalographers, St. Louis, Missouri, April 30, 1949, abstract in: *Electroencephalography and Clin. Neurophysiol.*, 1949, *1*:369.
13. Dusser de Barenne, J. G. and McCulloch, W. S. Kritisches und experimentelles zur Deutung der Potentialschwankungen des Elektrocorticogramms, *Ztschr. f.d. ges. Neurol. u. Psychiat.*, 1938, *162*:815.
14. Gibbs, F. A. and Hayne, R. The localizing value of electrical sign in electroencephalography, *Dis. Nerv. System*, 1948, *9*:289.
15. Lipton, B. and Gibbs, F. A. Effect of sodium cyanide on the human electroencephalogram, *Dis. Nerv. System*, 1948, *9*:135.
16. Gibbs, F. A., Gibbs, E. L. and Lennox, W. G. Electroencephalographic classification of epileptic patients and control subjects, *Arch. Neurol & Psychiat.*, 1943, *50*:111.
17. Gibbs, E. L., Gibbs, F. A. and Fuster, B. Psychomotor epilepsy, *Arch. Neurol. & Psychiat.*, 1948, *60*:331.

18. Gibbs, F. A. and Gibbs, E. L. Psychiatric implications of discharging temporal lobe lesions, *Tr. Am. Neurol. A.*, 1948, *73*:133.
19. Gibbs, F. A. and Gibbs, E. L. *Atlas of electroencephalography.* Cambridge, Mass., L. A. Cummings Co., 1941.
20. Cress, C. H. and Gibbs, E. L. Electroencephalographic asymmetry during sleep in patients with vascular and traumatic hemiplegia, *Dis. Nerv. System*, 1948, *9*: 327.
21. Gibbs, E. L. and Gibbs, F. A. Diagnostic and localizing value of electroencephalographic studies in sleep. *A. Research Nerv. & Ment. Dis. Proc.*, 1947, *26*:366.
22. Gibbs, F. A., Everett, G. M. and Richards, R. K. Phenurone in epilepsy, *Dis. Nerv. System*, 1949, *10*:47.
23. Bailey, P. and Gibbs, F. A. Preliminary report on temporal lobectomy for psychomotor epilepsy, read before the Missouri Neurological and Psychiatric Society, Oct. 1948.
24. Gibbs, F. A. and Gibbs, E. L. Positive 14 and 6 per second spikes: A new form of seizure discharge seen only in light sleep, reported before the Central Association of Electroencephalographers, Minneapolis, Minn., April 17, 1948.
25. Morison, R. S., Finley, K. H. and Lothrop, G. N. Spontaneous electrical activity of thalamus and other forebrain structures, *J. Neurophyiol.*, 1943, *6*:243.
26. Gibbs, E. L., Lorimer, F. M. and Gibbs, F. A. Clinical correlates of exceedingly fast activity in the electroencephalogram, *in preparation.*
27. Bailey, P. *Personal communication.*

A CHRONICLE OF ONE HUNDRED YEARS OF OTOLARYNGOLOGY*

A. C. FURSTENBERG

Professor of Otolaryngology, University of Michigan

To recount a century of otolaryngological achievements is to undertake a task of great magnitude and responsibility. An initial inquiry into the progress of otolaryngology during the past one hundred years reveals an extreme breadth of material that deluges any attempt at selection and baffles the preparation of a readable and coherent text. It is amazing to note the accumulation of bibliographic data of professional significance deposited within our otolaryngological storehouse during the past century. Obviously I cannot remove all of them, classify them specifically and work them into something of tangible educational value for practical usage. I can only hope to touch the high spots of one hundred years of advance, not in the form of a catalogue but more as a record in abstract of those accomplishments with which I can claim some personal experience.

An awareness of the impact of contemporaneous developments in medicine outside the field of pure otolaryngological discovery is a responsibility that must be faced in treating this subject. The science of otolaryngology has not grown and developed as an entity distinct and separate from the other sciences. To illustrate this point I need only mention the tremendous influence the discovery of the chemotherapeutic and antibiotic agents exerted upon otolaryngological diseases during the past decade. Sir Alexander Fleming's colossal discovery of the antibacterial effects of penicillin has revolutionized the practice of otolaryngology and altered it to such extremes that it now bears only a faint resemblance to its stature of a decade ago. Here we observe the tremendous effects of contemporary discovery. The acute infections of the pharynx, retropharyngeal abscess. peritonsillar abscess and the deep suppurations of the neck have nearly vanished. The acute inflammatory processes within the sinuses run a course of short duration and seldom

* Given before Centennial Meeting of The Section of Otolaryngology, April 16, 1947.

give rise to complications under the influence of the chemotherapeutic and antibiotic agents. The serious complications of mastoiditis which comprised a significantly important responsibility of otolaryngological practice and held the major interest of the members of our profession ten years ago are rarely in evidence today. The almost complete annihilation of temporal bone surgery and the marked decrease in the incidence of acute suppurative processes within the structures to which we give attention have prompted the statement many times in otolaryngological circles that otolaryngology has entered upon a period of decadence.

The future of otolaryngology is, however, by no means dark. There are great resources in this field which have not yet been tapped and these will be made available through scientific research. There are colossal opportunities for research in otolaryngology today, the promotion of which will open many new fields for practice. Consider if you will the unsolved problems of cancer, allergic reactions, nerve regeneration, the neurological manifestations of otolaryngological diseases, deafness and the rehabilitation of the hard of hearing; these and many others furnish innumerable investigative studies in which the joy of creativeness will be experienced by many of our colleagues and from which new methods of practice will be derived.

In the twenty year period from 1840 to 1860 there is little significant literature pertaining to the clinical aspects of the ears, nose and throat. Anatomical studies had been made but they were not correlated with clinical observations in any attempt to rationalize etiological influences and the behavior of disease. Isolated cases of epistaxis, sore throat and injuries to the ears and nose were described but records were brief and methods of treatment devoid of any vitality that would permit them to live beyond their time.

It must be acknowledged, however, that otorrhea was attracting the attention of some observers and exciting apprehension because of its potencies for serious complications. It was suspected at first that a discharge from the ear afforded "relief to some other local irritation." We find it stated that "in teething, ophthalmia, and other inflammations nature very commonly establishes this discharge which undoubtedly relieves these diseases." The evil consequences of chronic suppurative otitis media, namely, meningitis and brain abscess were becoming subjects of grave consideration. As one writer expresses, "the disease may

pass through the delicate organs of hearing, attack the membranes and even the substance of the brain producing then, and not till then, convulsions and death." One author recollects that "when a boy, in company with others, boys and men, a common amusement among them was to blow smoke from their segars they were using through their ears and a considerable percentage of these individuals in a country village could perform this feat."

While Phillip Bozzini, a German physician, announced in 1795 that he had conceived a means of performing endoscopy, he did not describe his endoscope until 1805. His invention received only scant attention and occasioned little interest until about forty years later when in 1843 an English surgeon, John Avery, described an instrument which visualized the vocal cords "better than it had ever been possible to see them before." Ten years later in 1853, Desormeau, a French physician in Paris, described an illuminated instrument of such practical value that historians have designated him the "Father of endoscopy." While the instruments and techniques for practical endoscopy upon living human subjects developed approximately one hundred years ago, the idea of examining the cavities of the body was posed some forty years before this period. It is another instance of one of the sad reproaches to the scientific world, namely, that many of our great discoveries go unnoticed and are lost to humanitarian service for many years after they have been made available to us. Sulfanilamide prepared in 1908 remained dusty on the organic chemists' shelves for a quarter of a century before it was recognized as a great savior of suffering and untold human lives. Similarly, penicillin was discovered in 1929, yet it remained obscure and attracted little attention until the pressure of demand was felt by the advent of World War II.

Mirror laryngoscopy was described in 1792 but the mirror as a diagnostic instrument was not employed to any great extent until its advantages were recommended by Czermak in 1858. Nearly ninety years have elapsed since this important but simple diagnosic procedure was recommended yet it is still neglected all too frequently by physicians in their routine daily practice. We continue to emphasize the great need of an early investigation of the causes of hoarseness, lesions which reveal their true identity in the vast majority of cases in the reflected image of the larynx in a mirror, yet hundreds of patients with operable carcinoma of the larynx come to grief yearly because of sheer neglect. It is another

instance of the obvious thing being the one most frequently overlooked.

In 1860 we begin to read an otolaryngological literature which departs from generalities and records something which is more concrete. Otolaryngologists began to focus their creative energy upon specific anatomical studies, etiology and the diagnostic signs and symptoms of disease. Joseph Gruber, Prussack, and Kessel studied the histology of the tympanic membrane, investigated its attachment to the handle of the malleus and the short process, and wrote in general on some anatomical considerations of the middle ear. These studies brought enlightment to the clinical behavior of disease, and inspired reports of acute and chronic suppurative processes in the temporal bone, and functional disturbances of the auditory mechanism. The role of the eustachian tube in admitting infection from the nasopharynx to the tympanum was recognized. Politzer's air douche was recommended after perforation of the tympanic membrane had occurred.

While the otolaryngologists of this age were familiar with the etiology and symptomatology of acute suppurative processes in the temporal bone and aware of their complications, they were obviously woefully in the dark in a knowledge of adequate treatment. But they were not without their convictions. In their characteristically professional manner they write succinctly and without fear of derision concerning the specific virtues of "half moon blisters, applied behind the ears and, an ear lotion of four grains of the acetate of lead to an ounce of water instilled into the ear, the use of mild astringent gargles, fluid extract of sarsaparilla, a teaspoonful internally twice a day, exercise in moderation, and the avoidance of coffee and most of the unnecessary stimulents."

In the 1870's we note that the conservative treatment of acute otitis media versus paracentesis of the tympanic membrane is a controversial issue. The literature records a great deal of acrimonious dispute on this matter even to the extent of severe ridicule and bitter imputations for those who resort to surgical measures. One writer in 1876 lays great stress on careful cleansing of the ear with an alkaline solution but vigorously opposes the paracentesis. He calls it a "fashionable" operation and concludes by analogy that if no oculist would perform a paracentesis of the anterior chamber for the sake of removing pus, then why should we approve of a paracentesis of the drum cavity for an acute inflammatory process of the middle ear.

In the next five years, 1870 to 1875, we find that the paracentesis became a popular method of treatment for acute suppurative otitis media. Many cases of acute inflammation of the middle ear treated by puncture of the drum head are briefly recorded but otolaryngologists continued to feel their way carefully in the treatment of temporal bone infections because we note that when signs and symptoms of acute mastoiditis put in their appearance, surgical efforts consisted only of an incision made through the skin down to the mastoid about one inch in length, one-half an inch behind and parallel to the attachment of the auricle. Obviously such a procedure was helpful in those neglected cases where the infection had perforated the mastoid cortex and had become active under the periosteum of the mastoid process. From ignorance of surgical techniques and in part too from the lack of courage, operations for acute mastoiditis were limited to a soft tissue incision and drainage.

The surgeons were soon to become bolder, however, because in 1879 a successful operation for acute mastoiditis is reported by opening the cortex of the mastoid bone. Dr. A. G. Gerster, a surgeon at the German Hospital and Dispensary, New York City, stated that he was describing this case in the literature "to encourage others to prompt action in similar instances." The operator deprecated the use of such instruments as the trocar and trepan because they could not be kept under observation and were therefore unsafe. He reports that "the employment of the chisel and mallet seems to offer the greatest security. Several advantages will accrue if the action of the chisel is tangential to the surface of the cranium: First, the bone will be opened layer by layer and thus laceration of the transverse sinus be best avoided; secondly, the cavity of the abscess is converted into a shallow basin that will afford excellent drainage." Schwartze had previously perforated the mastoid process with a drill but because he had been repeatedly deluded in his expectation of finding pus, there were often indications for a more extensive excavation of the mastoid process with chisel and spoon. In nearly all instances, however, we find that an operation upon the mastoid process was delayed while conservative measures were employed, particularly the application of leeches to the edematous swollen mastoid region.

We find in the literature of this period an appreciation on the part of otolaryngologists of functional ear diseases. The profession is cau-

tioned about the possibility of psychic conditions being reflected in the form of pain to the region of the ear and a warning is sounded not to interfere surgically with these patients. We read that "if the patient bears his pain badly, suffers from great depression of spirit, dwells to an extreme upon his illness, and is generally so much taken up with the severity of his pain as to have room for nothing else, we should hesitate to perform a surgical operation no matter how trivial it may be." The author goes on to say further: "we have no right, I think, to perform operations to clear up doubtful diagnoses; if in case the operation proves to have been unnecessary, the patient will be decidedly the worse for it." His admonition is given pedagogical emphasis when he states that "in teaching medical students, I have always found them when fully awakened to the danger of neglecting certain diseases to be more apt to do too much than too little, especially with the knife and active drugs."

In the time that has passed until the present day the importance of this warning has become no less significant than when it was expressed in 1879. The unending moral obligation of the profession to avoid surgical measures for diagnostic purposes and in patients with obvious psychogenic disturbances continues, I fear, to be treated lightly in our present day. We have come a long way in the development of surgical judgment since the above quotation was written but there is more to be learned and moral assessments to be made if we are to rank highly in the judgment of our professional colleagues.

It must be recorded that in 1876 Hartman opened the mastoid process through the external auditory canal with a drill. This was an early demonstration of the end-aural approach. Schwartze spoke most sharply against this technique because, as he warned, we then "drill into the darkness." Its advocates countered, however, by reciting the time-honored axiom that "when we become well acquainted with the anatomical relations many things will be illuminated that are now dark to us."

In the early 80's we discover that the nose and throat are beginning to attract attention and that the otolaryngologists of the day are advocating operations for the removal of hypertrophied adenoids and tonsils and the relief of nasal obstruction. The galvanocautery is recommended for the reduction of hypertrophied tonsils. The tonsil was gradually burned until the remaining portion was on a level with the palatine

folds. One or two areas were cauterized at each sitting and usually only one tonsil was operated upon at a time. From twelve to thirty sittings were required to complete the process and operators freely admitted that they noticed a disagreeable odor from sloughs and an impairment of appetite in consequence of their surgical efforts.

Other members of the profession questioned the utility of the galvanocautery, emphasizing the difficulties in the case of a struggling child who could not be induced to have a second sitting after the first painful experience. The dangers of ether in the presence of the galvanocautery were recognized and local anesthesia had not yet received popular approbation by the profession. Tonsillotomy was favored by many operators. The proponents of this procedure agreed that if they removed a thin slice of the gland they did no good whatever; but on the other hand, if more were removed grave hemorrhage might occur. One author explains that "too often this fact is applied as a sop to the conscience of timid operators and as an excuse for an incomplete operation. We should come down to the level of the pillars of the fossae but on the other hand we should not enucleate. The operation should be done with the tonsillotome; with bistoury there is greater risk of hemorrhage."

The submucous resection of the septum was preceded by an incredible number of destructive intranasal procedures, turbinates were sacrificed, the galvanocautery was used with subsequent stenosis and a variety of crushing procedures recommended to straighten the septum. One wonders why the simple yet most widely employed and singularly successful intranasal operation, the submucous resection of the septum, remained undiscovered until the turn of the century. In a most comprehensive paper presented at the 56th Annual Session of the American Medical Association in 1905, Dr. Otto T. Freer described the operation for submucous resection of the septum. The pervasive popularity and use of this operation seem to have been established shortly after this date.

Total extirpation of the larynx must have been a futile and discouraging operation in this period (the 1880's). Patrick Heron Watson of Edinburgh was the first to demonstrate the practicability of the operation in 1866 by performing it upon a patient, although the result was fatal due to a postoperative pneumonia. In 1883 Dillroth performed the laryngectomy at Vienna in sufficient numbers and with a degree of success that might entitle him to the credit of having made the opera-

tion a feasible procedure. The statistics of this age on total extirpation of the larynx for malignant disease are appalling. A table published in the Journal of Laryngology and Rhinology in 1887 records 103 cases; 40 died from the immediate effects of the operation. Others succumbed from inanition, pericarditis, lung abscess and septicemia within a few months until in the end there is recorded in this series only 9 out of 103 patients living twelve months after the operation. But in spite of these grievous results, the laryngectomy had ardent supporters in the 1880's. Many from the ranks of our specialty continued to study this problem and strove diligently to solve it. They met the challenge and through unity of thought and agreement directed a non-emotional approach to the various phases of this affliction and eventually established practical surgical procedures for the eradication of malignancy of the larynx. When one is reminded that for nearly three-fourths of a century leading apostles of laryngology have directed opinions to the real issues of laryngeal malignancy and tackled the job of surgical intervention step by step to find a cure, he is skeptical of the claims of success today made by the x-ray therapist of limited experience in this field. Too frequently surgical measures are unnecessarily delayed in the hope that palliative procedures will eradicate the disease. X-ray therapy is useful but it bears a minor relation to that conviction which governs my principles of procedure, namely, the necessity of operative interference when the larynx is the seat of an operable cancer. I am unwilling to compromise with any other recommendation and I hold the opinion that in most instances it is the most charitable method of treatment in that it minimizes suffering and gives greater assurance of longer survival.

While ether and chloroform have been used for approximately fifty years, we find considerable acrimonious dispute in the early 1890's in regard to the comparative toxicity of these two agents. Many of the hospitals in this country, even the large institutions in metropolitan areas had failed to keep records so that it was exceedingly difficult to compile statistics on the comparative advantages or disadvantages of ether and chloroform. As late as 1890 opinions gained from meager experience gave rise to the statement in some quarters that ether and chloroform were equally safe. It was generally agreed, however, that more dangerous symptoms had occurred when chloroform was used and that this anesthetic should be employed "in strong patients or when brain and

kidney diseases were present." Ether was advocated for "weak persons" but hospital records seem to indicate that chloroform was the anesthetic usually selected, probably because of its rapid action and because of failure as yet to appreciate its dangers.

An important advance in otolaryngology was the recognition and treatment of septic thrombosis of the cranial sinuses, resulting from suppurative disease of the middle ear and mastoid. To Zausal of Prague must be given the credit for the first therapeutic recommendation in 1880. He performed a ligation of the internal jugular vein in 1884 but his patient did not survive. Horsley of London, quite unaware of any previous effort to accomplish this technique, ligated the jugular vein in 1888, but his patient also met a fatal termination. The same year, Lane of England and Hoffman of Germany repeated the procedure previously recommended and were rewarded by successful results in both patients. When in 1889 to 1890 Ballance of London reported four cases with two recoveries, the operation was enthusiastically received by the profession and became a universal procedure in all countries where modern medicine was practiced. In the years that followed until the advent of chemotherapy and the antibiotics, a controversial issue was whether the operation should be restricted to a simple removal of the septic thrombus from the sigmoid sinus or extended to include a ligation or even a resection of the internal jugular vein. As far as I am aware this dispute was never settled to the satisfaction of the otolaryngological profession. It has obviously ceased to be an issue, however, since the incidence of lateral sinus thrombosis is infrequent and specific therapeutic measures are at our disposal. Although some impressive anatomical studies have demonstrated that there is a dense venous drainage through the tributaries of the jugular bulb and vein, and for this reason there was justification for skepticism concerning the effectiveness of jugular vein ligation, the operation nevertheless was frequently followed by phenomenal improvement of the patient. It seemed to be another instance of a septic process failing to follow the course anticipated from a study of practical anatomical considerations.

With the turn of the century we note that otolaryngologists in this country were performing complete operations upon the nasal accessory sinuses and instituting those principles of sinus surgery which are recognized to be the accepted ones of today. The technique which they advocated called for the complete eradication of all the diseased

processes, the meticulous removal of the lining mucous membrane of the sinus whether it be the maxillary, ethmoid, frontal, or sphenoidal sinuses, and the obliteration or maintenance of permanent drainage of the sinus cavity. Modern surgery is making more skillful approaches to the sinuses, reducing deformities to the minimum, and embellishing the techniques in some of their minor aspects, nevertheless, in the early 1900's the fundamental principles of sinus surgery were as well recognized and executed as they are by the surgeons of today. When the otolaryngologist's ingenuity failed him and this seemed to have occurred many years ago in surgery of the nasal accessory sinuses, he turned to the adornment of technical methods. The latter enriches the beauty of technique and enhances the interest of operators of varying degrees of skill but the end results in terms of service to the patient have gained nothing that was not accomplished by the procedures advocated and performed four decades ago.

We might span the period of twenty years from 1910 to 1930 by a simple glossary of significant otolaryngological advances. At the beginning of this period the value of roentgenology in otolaryngology was called to the attention of the American specialists. It was emphasized that the roentgenological diagnosis of sinusitis was based on the principle that the rays "passing through a bony cavity filled with air give the contrasting outline which is sufficiently different from that obtained when the air is replaced by secretion or granulation tissue." The roentgenologist was warned, however, that he "should not be tempted too far beyond this basic fact in his diagnostic ardor." It was emphasized then, as it is today, that close collaboration between the otolaryngologist and the roentgenologist would be productive of mutual understanding and consequent effective service to the patient.

About this time we were urged to give serious consideration to the faucial tonsils as a gateway to general infection. It was felt that many general infections developed from acute and chronic inflammatory disease of the tonsils, and that tonsillectomy was indicated in pericarditis, myocarditis, endocarditis, arthritis, chorea, neuritis, pleurisy, tuberculosis, iritis, phlebitis, osteomyelitis, Hodgkin's disease and possibly certain forms of leukemia. The pendulum of enthusiasm obviously swung too far and it required years of observation and study to prove that all these infections could not be charged to a tonsillar origin. This wave of interest in tonsillar sepsis probably had its virtues, however,

in that it made the otolaryngological profession cognizant of the fact that the lymphoid tissue of the pharynx is sometimes the portal of entry for the infections which produce swollen joints and damage the heart and kidneys.

For many years indirect laryngoscopy had been advocated. Then in 1914 we were urged to use the direct method in that it was a practicable procedure for children, overcame the handicap of the reversal of the image in a mirror, and could be employed for operative procedures under general anesthesia.

The possibilities and limitations of suspension laryngoscopy were described in 1916. It found favor in many clinics because it immobilized the patient and allowed freedom of both hands of the operator. About this same time the guillotine for tonsillectomy was recommended because of its speed, better cosmetic results, less bleeding, performance by the sense of touch and its practicability under nitrous oxide anesthesia.

In 1917 otolaryngologists were becoming apprehensive about the development of acute pulmonary abscesses, occurring after operative procedures on the upper air tract. Numerous explanations for this grave complication were offered including hematogenous and lymphogenous spread of infection. It is a significant fact, however, that improved methods of anesthesia and adequate suction of the operative fields have greatly reduced the incidence of this hazard. Direct gravitation of infected material into the lower air passages must have been the responsible influence in most of these cases.

In the period from 1910 to 1930 I am impressed also by the fads and fancies in otolaryngology. Might it not be truthfully stated that the eye complications arising from diseases of the nasal accessory sinuses, particularly iritis, choroiditis, and retrobulbar optic neuritis were over emphasized? Did we not stress too radically the occurrence of sinusitis in infants and children and perform many unnecessary operations upon patients in the early years of their growth? Were we not led astray by the presumption that asthma was the result of a nasal reflex and that radical operations upon the nasal accessory sinuses for the removal of polypoid disease were curative measures? It is doubtful that there are any votaries of this theory today. Time and experience have obviously placed them in an ignominious position because the contentions of 1930 in regard to the relation of asthma and

chronic sinusitis have not been sustained. Convictions of the existence of a spheno-palatine ganglion syndrome were fleeting; early opinions on the advantages and disadvantages of the various local anesthetics in the nose and throat have not stood the test of clinical and pharmacological investigation, and the occurrence of deafness in patients with vitamin deficiencies has not been substantiated by scientific studies of an acceptable character. While these may have been some of the whims of the profession, they perhaps had their virtues in that they evoked academic interest and in some instances gave rise to theories which were reduced to facts for practical usage in otolaryngology.

To French radiologists belongs the credit of the first use of lipiodol and its introduction to roentgenologic practice. About 1927 the employment of a radiopaque substance in the visualization of the lower air passages was established in this country as an aid to the diagnosis of bronchial and pulmonary disease. It opened a wide field of study from both a diagnostic point of view and the teaching of practical anatomy.

In the literature of the 1920's we observe a growing interest in hay fever and the clinical manifestations of allergy. The cutaneous or scratch method of testing patients for pollen reactions was gaining favor and thorough surveys of botanical flora were being made at certain seasons of the year in many parts of the country. It was the beginning of a specialty in which reputations were to be made and yeoman service rendered to patients afflicted with a condition that heretofore had resisted all forms of local therapy.

In 1922 our attention was called to the disease agranulocytic angina although the etiological influences responsible for this condition were not understood. Attempts to find a specific organism invariably failed. The condition of the bone marrow, however, gave some evidence that the disease was probably due to a toxin that destroyed the granulocytic blood cells and inhibited the blood forming centers of the bone marrow. My memory is still vivid of several tragic cases seen on our wards about this time; patients with agranulocytic angina to whom repeated doses of pyramidon were administered for headache and general discomfort.

Until this period of the 1920's our popular text books had taught that primary carcinoma of the lung was exceedingly rare. Improved instruments and bronchoscopic technique were beginning to demon-

strate that this condition was by no means as rare as formerly stated. In the previous decade the diagnosis had been made at autopsy; now we were beginning to observe the true identity of the lesion through the bronchoscope. There seems little doubt now that we are experiencing an actual increase in malignancy of the lung and not a relative one due to more precise methods of diagnosis.

A better understanding of acute suppurations of the mediastinum and the procedure of cervical mediastinotomy greatly reduced the mortality from this disease in the late 1920's. In 1931 petrositis was revealed as an entity and understood both in regard to the pathology of spread of the infection and the technical procedures for adequate drainage. It should be regarded one of the great contributions to otology, a savior of suffering and lives from the period of the early 1930's to the advent of chemotherapy and the introduction of the antibiotics.

Although modern otolaryngology may be said to have antedated the advent of chemotherapy, it must be admitted that the introduction of the sulfonamides gave rise to a changed point of view in respect to the practice of our specialty. Proof of this fact was the often repeated statement by authorities that chapters in our text books would need to be rewritten. We observed an abrupt shift from discussions of inflammatory processes to such studies as the physiology of the nose, neurological lesions which influence the various senses, plastic surgery, the embryological derivations of tumors and cysts, and noteworthy investigations of disturbances of the auditory function and the facial nerves.

Important advances have been made within recent years in our understanding of Ménière's disease. We now recognize it to be a hydrops of the otic labyrinth, a condition which occasionally responds satisfactorily to different forms of medical therapy. No doubt, too, it is prone in some instances to undergo spontaneous intermissions or remissions. Surgical procedures upon the labyrinth, as for example, decompression and electrocoagulation, have given results of promise equal to those obtained from a subtotal section of the auditory nerve.

We have experienced two World Wars within the past one hundred years but a review of otolaryngological practice during both of them leaves one with the impression that noteworthy accomplishments were not conspicuous by their number. This is to be expected when one recalls that most otolaryngological staffs in various teaching centers

were greatly reduced by a call to military service and the personnel which remained in civilian practice were overwhelmed by routine responsibilities in the care of the sick. More significant perhaps is the fact that special emphasis was placed upon fields of research which did not fall within the province of otolaryngology. The war demanded that particular attention be given to investigations pertaining to the prevention and treatment of infectious diseases, the care of the wounded, psychiatric disturbances and physiologic problems which arose as the result of placing individuals in abnormal environments.

In spite of the rather undignified position our specialty assumed in military service and in spite of the fact that otolaryngologists in general were subordinated to other professional personnel in the army, the members of our profession saw their responsibilities and gave their unfailing support to the job at hand. One evidence of devotion was seen in aviation medicine. The influence of radium in the prevention and treatment of anomalies of pressure within the middle ear was well known prior to the war and it remained, therefore, for members of our specialty to recognize its indications and to employ it effectively in conditions occurring among aviation personnel.

Nerve grafting and nerve anastomosis attracted the interest of members of our profession and led to the development of surgical techniques more practicable in their application and productive of greater success than attained at any previous time. Men fundamentally trained in the anatomy and pathology of the temporal bone led the way to memorable progress in this field.

In the study of acoustic trauma, interesting advances were made during the war by representatives from our ranks. While injury to the auditory function did not become a problem of great magnitude, it must be granted that otolaryngologists were quick to respond to the request from military authorities for a better understanding of this condition.

I point with pride and with a deep sense of gratitude to those farsighted and efficient otolaryngologists in military service who created an epochal program of service in the army and navy centers for the rehabilitation of the hard of hearing. They achieved phenomenal progress and rendered a service that will go down in history as one of the brilliant examples of humanitarian efficiency during the war. Advances among civic agencies are usually conspicuous by delay but I venture

the opinion that the impetus given this magnificent program of service to the hard-of-hearing by military personnel is destined to inspire, if not demand, a similar plan of action in civilian life.

It is encouraging to observe within the past decade that our profession is endeavoring to offer something more to the public than elaborate programs of prevention and expansive statistical compilations in the field of impaired hearing. Otolaryngologists and workers in the acoustic sciences are now wisely directing attention to the significant problems of deafness and formulating programs of therapy which give promise of real service to the hard-of-hearing. Thanks to recent studies, otolaryngologists are now equipped with the means of producing an atrophy and retrogression of lymphoid tissue responsible for anomalies of pressure within the middle ear. The use of radium in this type of deafness is an epoch in the progress of therapy and gives hope of saving or restoring serviceable hearing to children in whom the pathological changes in the tympanum are due to an occlusion of the eustachian tubes by lymphoid tissue.

There is justification it seems to me for the present widespread interest in the surgical treatment of otosclerosis. The one stage operation stands today as the only therapeutic measure which has been of service to patients with this disease. The fenestration operation constitutes a magnificent contribution to this field, not only because it has given serviceable hearing to some of the unfortunate victims of otosclerosis, but for the reason too, that it has inspired a deeper interest in the anatomy of the temporal bone and brought together some sincere and intelligent persons from the ranks of the medical sciences to study this problem and find its solution. From this operation, observations have been made and theories have been derived. There is a good chance that by further careful experimentation some of these theories will be reduced to facts.

I cannot pass by without mention the noteworthy progress our specialty has made in the training of young men in otolaryngology. Education above the level of undergraduate studies is not only a mark of the medical profession but a significant requirement that has assumed increasing importance with the evolution of American medicine. Its progress has not been rapid nor has it yet achieved exemplary objectives, nevertheless, it has developed resolutely into an essential program that demands the attention of all graduates of medicine today.

Most of us can remember that less than three decades ago the general rotation internship was not considered essential to the practice of medicine, nor was it required by our State Boards of Registration for licensure. Today no young graduate would attempt medical practice without at least one year of internship, nor would the young doctor venture to apply for the study of a specialty without completing the intern year because he knows that this requirement is imposed by all reputable graduate medical schools and departments in this country. Thus we find that the rapid progress which medicine has made in recent years, particularly its advances in the field of specialization, has initiated a public demand for technical skills and specialized capabilities that can be furnished only by the individual who keeps in stride with continuing education throughout his lifetime of useful service.

One of our greatest advances in the education of the otolaryngologist has been the establishment of curricula of continuing study which offer training to staff members for a three, four, or even five year period. In these groups there are students of varying degrees of experience and skill who transmit their knowledge of the subject to those whom they outrank and receive instruction in turn from the superior officers on the staff. Thus each member of the group assumes the function of an instructor and the responsibilities thus imposed upon him are invariably followed by a diligent search for knowledge and information which he may pass on to those whom he is expected to serve.

But let me warn that the otolaryngologist of today must assume certain educational responsibility before he commences the practice of his specialty. He must be thoroughly trained in the principles of surgery, newer surgical techniques, protein metabolism, the recognition and treatment of shock, the value of early ambulation, methods of resuscitation therapy, and the use of modern anesthetics, if he is to practice surgery of the head and neck with credit to himself and safety to his patient. Recent progress in surgery has demonstrated that the preparation of the patient has much to do with the manner in which he tolerates a surgical insult and his behavior during the period of convalescence. Too much emphasis cannot be placed upon the protein requirements of the surgical patient. The degree and rate of tissue repair are tremendously influenced by the aminoacids and any patient who is a victim of their impoverishment is destined to react poorly to a major surgical procedure.

Experience during the war taught us that the best treatment for blood loss was a transfusion of whole blood. Chemotherapy and penicillin when intelligently used are great saviors of life and limb, but are not substitutes for operations properly performed. These agents are not a compromise for a poor operation and anyone who believes that the sulfonamides used locally will compensate for mediocrity in the operating room is certain to be disillusioned. The trend now is definitely against the introduction of the chemotherapeutic agents directly into a wound.

Throughout this discussion there has been a great temptation to quote from numerous references and to pose the viewpoints of many otolaryngologists who have made creditable contributions to the literature. I wish it might have been possible to pay tribute to our living contributors and to do justice to them by expressing their critical judgments, but time obviously would not permit such an encyclopedic survey of the past century of otolaryngology. Unquestionably I have overlooked many important and significant advances during this period. If I have failed in some instances to give correct dates, it is because I have not tried to identify the time of ideas and concepts; rather have I endeavored to date the periods of changing trends and the practical application of them. If there is any justification for this long review, I hope it may be found in a deeper appreciation of the indomitable spirit and devotion of our forefathers and a motivation to the young men of today in whose hands the fate of otolaryngology is held, to strive even more sedulously for future progress.

SECTION ON MICROBIOLOGY

WEDNESDAY EVENING, APRIL 20, AT 8:30 O'CLOCK

I. EXECUTIVE SESSION

a. Reading of the Minutes

b. Election of Section Officers

For Chairman—Frank L. Horsfall, Jr.

For Secretary—Harry Most

c. Election of one member of the Advisory Board

Gregory Shwartzman (1949-54)

II. PAPERS OF THE EVENING

a. Chemistry of chloromycetin
H. M. Crooks, Jr. (by invitation)
Parke Davis Research Laboratories
Detroit, Michigan

b. Clinical use of synthetic and fermentation chloromycetin
Joseph E. Smadel (by invitation)
Army Medical School
Washington, D. C.

c. Clinical use of chloromycetin in certain bacterial infections
Theodore E. Woodward (by invitation), University of Maryland School of Medicine, Baltimore

GREGORY SHWARTZMAN
Chairman
The Mount Sinai Hospital

HARRY MOST
Secretary
New York University
College of Medicine

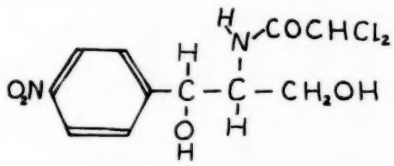
Chemistry of Chloromycetin

H. M. CROOKS, JR.

At the risk of being somewhat inadequate in treatment of the subject I have taken the liberty of changing the emphasis in this talk. For an audience of physicians the purely organic chemistry phases of the development of this antibiotic could be most boring. I trust I shall be forgiven for only pointing out some of the salient features of the chemistry and treating at more length the toxicologic features and the metabolism as they have been worked out by my colleagues, Drs. Gruhzit and Glazko and their groups.

In our screening of various organisms from soil samples Ehrlich and his group found that an actinomycete selected from a Venezuela soil sample by Burkholder of Yale produced a considerable antibiotic activity which appeared to be new in its antibacterial spectrum. Moreover, it proved intriguing to the chemist, when Bartz succeeded in isolating and crystallizing the active material with a reasonable melting point of 150°, stable enough to be sublimed in high vacuum, stable over a pH range of 3 to 9 in solution and of a molecular weight, about 310, well within the range of synthesis. The compound is optically active and, from analysis, has the formular $C_{11}H_{12}N_2Cl_2O_5$. The fact that the chlorine was not ionic in nature but actually quite inert chemically was most interesting. The substance also showed a strong absorption band in the ultra-violet region. Two of our staff, Doub and Vanderbelt, have devoted considerable study to the relation of such absorp-

tion to structure. We were politely skeptical when they told us that the compound looked like a derivative of *para*-nitro-toluene. We were quite aware that nitro-groups have never been found in nature or associated with living processes excepting in a toxic manner. Our apologies were given in all humility when the structure as finally determined by Dr. Mildred Rebstock proved to be a para-nitrophenylpropane derivative:



Chloromycetin

D-(—)-*threo*-2-dichloroacetamido - 1 - *p*-nitrophenyl-1,3—propanediol.

Structurally the carbon skeleton shows a resemblance to *nor*-ephedrine but here again the antibiotic activity is associated with "unnatural" optical form as in penicillin with its "d" amino acid component. The Chloromycetin structure is related to *l-pseudo-nor*-ephedrine and not to *l*-ephedrine. The appearance of dichloroacetic acid as the amide on the side-chain was also almost as unexpected as the nitro-group.

With the knowledge that we were dealing with a nitro-phenyl compound which was a derivative of an unpleasantly corrosive organic acid you can understand that toxicity data were examined most critically. It just did not seem reasonable that Chloromycetin should be non-toxic. We will get to that story shortly.

Almost as soon as we were sure of the structure of the carbon skeleton Controulis started to work on synthesis. He acquired quite a knowledge of the difficulties of preparing a compound with a number of functional groups. The synthesis which he developed started with benzaldehyde and nitroethanol and was quite successful on a laboratory scale but presented some difficulties for large scale production. Alternate methods using a different series of reactions and starting either from benzaldehyde or acetophenone were developed by Long and Troutmann and these are now being expanded to production scale. While consideration of the structure of the antibiotic shows that four optical forms can (and do) exist, the synthetic material now being produced is identical in all respects, physically, chemically and biologically, with the drug as produced by fermentation. It is the first practical synthesis of a major antibiotic.

To revert to the matter of toxicity, Chloromycetin has proved to be essentially non-toxic in therapeutic doses. The acute toxicity in mice, intraperitoneally in acacia suspension, shows a maximal tolerated dose of 750 mg/kg., LD_{50} 1320 mg/kg; orally, 1500 mg/kg and 2640 mg/kg respectively. Intravenously, in rats, using a solution in 50% acetamide the maximal tolerated dose is 225 mg/kg and the LD_{50} dose about 280 mg/kg. In dogs, orally, the tolerated dose is about 300 mg/kg and we have not yet found the dosage level which is 50% lethal. In chronic toxicity studies mice have tolerated 425 mg/kg/day for 4 weeks with the LD_{50} level somewhere over 2060 mg/kg/day when given in the ration for two weeks. Dogs have tolerated over 200 mg/kg/day for 4 months. Again in this species we have not yet been able to reach the LD_{50} level orally.

When administered intravenously in propylene glycol (10% solution) to anesthetized dogs at the rate of 2 cc. per minute a 100 mg/kg dose of Chloromycetin shows little effect on respiration but a definite effect on blood pressure, inducing a fall in blood pressure of the shock type.

Dogs on an oral dosage of Chloromycetin up to 100 mg/kg/day show a slight drop in erythrocyte count over a three month period, from about 6.7 to 6.0 million, hardly more than would be expected in untreated dogs bled of 100 cc. three times in the same interval.

Examination of the blood non-protein nitrogen of eleven dogs given 50-100 mg/kg/ twice daily for 4½ months showed no more variation than is to be expected on a similar random group of pound animals.

Turning now to the fate of Chloromycetin

in the animal body, it was found quite early that the drug is readily absorbed when given orally and significant blood levels are obtained promptly. In dogs a level of 20 micrograms per cc. is obtained one hour after a 150 mg oral dose, a peak at about 40 micrograms is obtained at four hours which drops below 10 micrograms only after eight hours. In contrast a 50mg/kg intravenous dose starts at the 40 microgram level falling below 10 in about 3 hours. When the urine of these dogs is examined it is found that the peak excretion for orally administered drug is at about 4 to 6 hours and that only small amounts are being excreted after 20 hours. It was interesting to find that only about 3-7% of the administered activity was recoverable in the urine. On the other hand if the urine were assayed chemically to determine the nitro-compounds excreted the 150mg/kg orally dosed dog eliminated 55% of the drug in the urine.

It was found that man showed an even higher efficiency in quantitative elimination of the drug in the urine. Again an oral dose of 1500 mg. showed a peak in serum levels at about the 4 hour period, effective levels being maintained for from 6 to 8 hours. Examination of the excretion rate data after an oral dose of 500 mg. showed that roughly half had been excreted by eight hours and only small amounts remained at 24 hours. About 7½% of the dose was recoverable as biologically active unchanged drug but 91% of the original amount of nitro-compound was recovered. Glazko and his group set about isolating the metabolized portion. It turned out to be a compound much more soluble in water than Chloromycetin and not, strictly, a degradation product. Instead of chewing the antibiotic up into little pieces where the nitro group could more readily exert its toxic effects, the animal body apparently moves it out of its system as the sodium glucuronide through conjugation of one of the hydroxyl groups with glucuronic acid, the remainder of the molecule, including the amide linkage, surviving intact.

While I have mentioned many of the workers identified with the development of Chloromycetin there have been many omissions. The nature of antibiotic research calls for an integrated team of bacteriologists, biochemists and chemists both in research and development scale and the listing here would be a long one. This glimpse of the laboratory end of the problem is, after all, the preliminary to the meat of the story, the clinical test of the drug. We hope and believe that that part will be quite as fascinating as ours.

Clinical Use of Synthetic and Fermentation Chloramphenicol (Chloromycetin)

JOSEPH E. SMADEL

The new antibiotic chloramphenicol has proven extremely useful in the treatment of a number of the rickettsial diseases of man. These include epidemic and murine typhus, scrub typhus, and Rocky Mountain spotted fever. In most of these rickettsial infections, which previously had been only moderately amenable to treatment with para-aminobenzoic acid, patients receiving chloramphenicol became afebrile in a day or so after therapy was instituted.

The new synthetic form of chloramphenicol, which has been studied extensively in the laboratory and on the ward, possesses the same antirickettsial properties as the fermentation type drug. Furthermore, the synthetic compound is of the same low toxicity for man as the natural material obtained from the fermentation of *Streptomyces venezuelae*. Charts illustrating the results obtained in the treatment of patients with rickettsial diseases were presented and discussed.

Clinical Use of Chloramphenicol (Chloromycetin) In Certain Bacterial Infections

THEODORE E. WOODWARD

Certain diseases of bacterial origin have responded to treatment with chloramphenicol in a highly uniform and specific manner. These include typhoid fever, undulant fever and several infections of the genito-urinary tract.

Twenty-two patients with typhoid fever received chloramphenicol on the 12th day of illness (mean). The average duration of fever after receiving treatment was 3.5 days. Four patients in this series with bacterial and clinical relapses responded to retreatment. Four typhoid carriers have not benefited from chloroamphenicol therapy. Nine patients with acute brucellosis treated on the 33rd day of illness (mean) responded within 3 days. One patient relapsed but promptly responded to a second course of antibiotic. Patients with chronic urinary tract infection, caused by bacteria of the colon, proteus and pseudomonas groups have also benefited from treatment with this drug.

RECENT ACCESSIONS TO THE LIBRARY

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Abernethy, J. L. Principles of organic chemistry. Phil., Saunders, 1949, 317 p.

Aggeler, P. M. & Lucia, S. P. Hemorrhagic disorders. [Chic.], Univ. of Chic. Press, [1949], 111 p.

Alberti, V. A. J. La presión de la arteria pulmonar. Buenos Aires, El Ateneo, 1948, 170 p.

d'Ávila, S. Prolapso e procidência do reto. Rio de Janeiro, Livraria Odeon, 1947, 208 p.

Barbier, J. Émotion, émotivité, constitution émotive. Lyon, Voix et Visions, [1947], 166 p.

Beaux, A. R. Injertos de piel. Buenos Aires, El Ateneo, 1947, 257 p.

Berger, F. Handbuch der Drogenkunde. Wien, Maudrich, 1949, v. 1.

Beyer, W. Verletzungen und Erkrankungen im Bereich des Schultergürtels. Stuttgart, Wissenschaftliche Verlagsgesellschaft, 1947, 174 p.

Boshamer, K. Die postoperative Behandlung chirurgisch Kranker durch den praktischen Arzt. Stuttgart, Wissenschaftliche Verlagsgesellschaft, 1948, 130 p.

Brown, G. T. Pollen-slide studies. Springfield, Ill., Thomas, [1949], 122 p.

Bruens, E. Sulfonamide und Penicillin; örtliche Anwendung in der Augenheilkunde. Stuttgart, Wissenschaftliche Verlagsgesellschaft, 1948, 138 p.

Bürki, E. Das Haftglas als optisches Instrument. Basel, Karger, 1948, 322 p.

Búlfaro, J. A. H. Fracturas del extremo inferior del radio. Buenos Aires, Editorial Universitaria, 1947, 243 p.

Calatroni, C. J.; Ruiz, V. & di Paola, G. Endocrinología sexual femenina. Buenos Aires, El Ateneo, 1947, 724 p.

Claye, A. M. Management in obstetrics. London, Oxford Univ. Press, 1948, 186 p.

Cowie, A. T. Pregnancy diagnosis tests. Shinfield, [Commonwealth Agricultural Bureaux], 1948, 283 p.

Cullen, S. C. & Gross, E. G. Manual of medical emergencies. Chic., Year Book Publishers, [1949], 267 p.

Curschmann, H. H. Lehrbuch der speziellen Prognostik innerer Krankheiten. 3.Aufl. Stuttgart, Enke, 1948, 304 p.

Deluca, F. A. Origen de los gemelos univitelinos. Buenos Aires, [Ferrari], 1948, 215 p.

Fairhall, L. T. Industrial toxicology. Balt., Williams, 1949, 483 p.

Frobisher, M. Fundamentals of bacteriology. 4.ed. Phil., Saunders, 1949, 936 p.

González Loza, M. Endoscopia peroral. Buenos Aires, El Ateneo, 1947, 610 p.

González Warcalde, J. Anatomía patológica de la tuberculosis del aparato digestivo. 2.ed. Cordoba, Rep. Arg., Lutz, 1947, 164 p.

Grund, G. Dia Anamnese; Psychologie und Praxis der Krankenbefragung. 2.Aufl. Leipzig, Barth, 1947, 240 p.

von Haberer, H. Die Erkrankungen der Leber und der Gallenwege. Kempen-Niederrhein, Thomas, 1947, 199 p.

Hirsh, J. The problem drinker. N. Y., Duell [1949], 211 p.

Holmes, S. J. Organic form and related biological problems. Berkeley, Univ. of California Press, 1948, 169 p.

Huneke, F. Krankheit und Heilung anders gesehen. 7.Aufl. Köln, Staufen, [1948], 273 p.

Jeanneney, G. & de Grailly, R. Formulaire vitaminothérapique du praticien. Paris, Doin, 1948, 202 p.

Jordan, E. O. & Burrows, W. Textbook of bacteriology. 15.ed. Phil., Saunders, 1949, 981 p.

Kantor, J. L. & Kasich, A. M. Handbook of digestive diseases. 2.ed. St. Louis, Mosby, 1949, 658 p.

Kehrer, F. A. Die konstitutionellen Vergrösserungen umschriebener Körperabschnitte. Stuttgart, Thieme, 1948, 293 p.

Khoury, C. Hallux valgus. Buenos Aires, López, 1947, 227 p.

Kienle, F. Diphtherische Herzkomplikationen. Stuttgart, Wissenschaftliche Verlagsgesellschaft, 1947, 167 p.

Kleinschmidt, O. Operative Chirurgie. 3. Aufl. Berlin, Springer, 1948, 1545 p.

Krabbe, K. H. Nervelidelser og vaextforstyrrelser i barndommen. København, Munksgaard, 1947, 368 p.

Lamy, M.; Lamotte, M. & Lamotte-Barrillon, (Mme.) S. La dénutrition. Paris, Doin, 1948, 407 p.

Lemkau, P. V. Mental hygiene in public health. N. Y., McGraw-Hill, 1949, 396 p.

Mackenzie, C. F. The miracle of homoeopathy. London, Homoeopathic Pub. Co., [1948], 108 p.

Meyer, R. Autobiography of Dr. Robert Meyer (1864-1947). N. Y., Schuman, [1949], 126 p.

Montpellier, P. J. M. Autour du problème du cancer. Alger, Ferraris, 1944-1948, 2 v.

Münchener klinisches Rezepttaschenbuch, hrsg. von H. Braun und F. Steigerwaldt. Stuttgart, Wissenschaftliche Verlagsgesellschaft, 1948, 864 p.

New York Academy of Medicine. Centennial. Institute of Medical Education. Trends in medical education. N. Y., Commonwealth Fund, 1949, 320 p.

Noguer Molins, L. Diagnóstico médico. 4.ed. Barcelona, Editorial Científco Médica, 1949, 708 p.

Operative technic in general surgery, edited by W. H. Cole. N. Y., Appleton-Century, [1949], 951 p.

de Paternina, M. Amigdalitis crónica. Barcelona, Editorial Labor, 1948, 356 p.

Pharmacology and toxicology of uranium compounds, edited by C. Voegtlin and H. C. Hodge. N. Y., McGraw-Hill, 1949, 1 v. in 2.

Pindborg, J. J. De hårde tandvaevs normalhistologi og patologi. København, Munksgaard, 1948, 132 p.

Piqué, J. A. & Schajowicz, F. Tumores de los huesos. Buenos Aires, El Ateneo, 1948, 94 p.

Prather, G. C. Urological aspects of spinal cord injuries. Springfield, Ill., Thomas, [1949], 146 p.

Prévôt, R. Grundriss der Röntgenologie des Magen-Darmkanals. Hamburg, Nölke, 1948, 199 p.

Rat (The) in laboratory investigation, edited by E. J. Farris and J. Q. Griffith, jr. 2.ed. Phil., Lippincott, [1949], 542 p.

Regan, L. J Doctor and patient and the law. 2.ed. St. Louis, Mosby, 1949, 545 p.

INDEX, 1949

Abramson, Harold A., Therapy of asthma with reference to its psychodynamic pharmacology, 345
Accessions to the Library, Recent, 61, 130, 264, 331, 397, 537, 601, 666, 795
Address of acceptance and appreciation of the gift of the Edwin Smith papyrus, George Baehr, 60
of the retiring president, George Baehr, 145
of welcome to 22nd Graduate Fortnight, advances in diagnostic methods. Benjamin P. Watson, 747
Adlersberg, David, Newer advances in gout, 651
Advances in diagnostic methods, Benjamin P. Watson, 747
in our knowledge concerning the etiology and treatment of hematological disorders, Cyrus C. Sturgis, 84
in therapy, George Baehr, 3
in treatment of malignant disease, C. P. Rhoads, 271
Allen, Frederic M., Discussion on Review of studies on blood sugar, 52
Allergy and antihistamine therapy, a review, Mary Hewitt Loveless and Milton Dworin, 473
Ambulation, Early, following surgical procedures, James B. Blodgett, 176
Analgesic drugs, New, Henry B. van Dyke, 152
Antiepileptic drugs, Use of, H. Houston Merritt, 5
Anti-histamine substances, Recent advances in the domain of the, phenothiazine derivatives, B. N. Halpern, 323
Antihistamine therapy, Allergy and, a review, Mary Hewitt Loveless and Milton Dworin, 473
Annual meeting, January 6, 1949
Address of the retiring president, George Baehr, 145
Presidential address, Benjamin P. Watson, 135
Results of operations for hyperparathyroidism, William Barclay Parsons, 285
Appraisal of the clinical aspects of the Rh factor, Peter Vogel, 261
Ashford, Mahlon, The New York Academy of Medicine, its first hundred years by Philip Van Ingen, a review, 741
Asthma, Therapy of, with reference to its psychodynamic pharmacology, Harold A. Abramson, 345

Bacteria, Relationship of, to the common cold, Yale Kneeland, Jr., 534
Bacterial infections, Clinical use of chloromycetin in certain, Theodore E. Woodward, 795
Baehr, George, Address of acceptance and appreciation of the gift of the Edwin Smith papyrus, 60
Address of the retiring president, 145
Advances in therapy, Opening address Graduate Fortnight, 1948, 3
Bell's and other palsies, Treatment of, William Bierman, 307
Best, Charles H., Discussion on Review of studies on blood sugar, 58
Bierman, William, Treatment of Bell's and other palsies, 307
Biggs (Hermann M.) Memorial Lecture, Medical, social and public health aspects of rehabilitation, Howard A. Rusk, 554
Blodgett, James B., Early ambulation following surgical procedures, 176
Blood sugar, Review of studies on, Edward Thomas Waters, 32
Discussions, Frederick M. Allen, Edward M. Dillon, Thomas H. McGavack and Charles H. Best, 52
Book review
The New York Academy of Medicine, its first hundred years by Philip Van Ingen, review, Mahlon Ashford, 741
Browder, Jefferson, Pain in the lumbo-

sacral region, 434
Bruger, Maurice and Elliot Oppenheim, Present status of liver function tests including observations on the newer flocculation procedures, 16

Cancer research, General view of, Leonard A. Scheele, 671
Centennial addresses
Chronicle of one hundred years of otolaryngology, A. C. Furstenberg, 775
Psychiatric perspectives of today, Gregory Zilboorg, 577
Thoughts on medical history and libraries—1847 and 1947, Sanford V. Larkey, 65
Central nervous system, Modern treatment of syphilis, including syphilis of the, Evan W. Thomas, 505
Chemical aspects of some of the newer insecticides, H. L. Haller, 374
Chemistry of chloromycetin, H. M. Crooks, Jr., 792
Chloramphenicol. See Chloromycetin.
Chloromycetin, Chemistry of, H. M. Crooks, Jr., 792
Clinical use of synthetic and fermentation, Joseph E. Smadel, 794
in certain bacterial infections, Clinical use of, Thomas E. Woodward, 795
Chronicle of one hundred years of otolaryngology, A. C. Furstenberg, 775
Clinical aspects of some of the newer insecticides, H. L. Haller, 374
use of chloromycetin in certain bacterial infections, Theodore E. Woodward, 795
use of synthetic and fermentation chloromycetin, Joseph E. Smadel, 794
Clinical Research Meeting (abstracts)
Anomalous atrioventricular excitation produced by catheterization of the normal human heart, Bertha Rader, Adolph R. Berger, Stanley A. Briller, Joseph Brumlik and Charles E. Kossmann, 444
Association of interatrial septal defect and anomalies of the osseous system, B. S. Oppenheimer, N. S. Blackman and Arthur Grishman, 442
Aureomycin and chloromycetin in brucellosis, Harold J. Harris, 458
Autoantibodies in different phases of human glomerulonephritis, Kurt Lange, David Weiner, Michael M. A. Gold, Victor Tchertkoff and Vera Simon, 447
Biological chemistry of wound healing, effect of blocking the sulfhydryl group (-SH) in vivo with iodoacetic acid, Jameson L. Chassin and S. Arthur Localio, 452
Carbohydrate utilization in surgical patients, blood lactic acid in pre- and post-operative patients after the administration of glucose, John J. Castronuovo, 455
Effect of an adrenolytic compound, dihydroergocornine, on epinephrine-induced stimulation of the adrenal cortex, Stanley August and Richard Gubner, 446
Electrolyte abnormalities in chronic congestive heart failure, effects of administration of potassium and sodium salts, Charles L. Fox, Jr., Charles K. Friedberg and Abraham G. White, 461
Ergotamine tartrae and the "2-step" exercise electrocardiogram in functional heart disturbance and in organic heart disease, Leon Pordy, Joseph Kolker, Mortimer J. Blumenthal and Arthur M. Master, 445
Evaluation of the mumps skin-test in pediatric practice, Alfred L. Florman, Alfred E. Fischer and Ralph E. Moloshok, 441
Fate of dicumarol in man, relationship between prothrombin time and plasma level of dicumarol, Murray Weiner, Shepard Shapiro, Julius Axelrod and Bernard B. Brodie, 449
Hemophilioid disease, O. Herman Dreskin and Nathan Rosenthal, 457
Hypermetabolism without hyperthyroidism, Solomon Silver, Edward B. Crohn and Philip Porto, 441
Management of ascites due to cirrhosis of the liver, the use of "rice" diet, blood and plasma, diuretics and surgery, George F. Kamen, Max Trubek and Jere W. Lord, Jr., 454
Method for the preparation of exteriorized skin covered loops of intestine for the study of bowel obstruction,

Robert T. Crowley and Donald A. Davis, 450
New synthetic anticoagulant (heparinoid), preliminary report of its action in humans, C. W. Sorenson, Joseph Seifter and I. S. Wright, 448
Response of gastric-dissolved mucoprotein to insulin, a new test for evaluation of secretory status of fundal glands and integrity of nervous pathways to the stomach, George B. Jerzy Glass and Linn J. Boyd, 459
Role of proteins in the pathogenesis of renal insufficiency, Ralph M. Sussman and Selwyn Z. Freed, 462
Significance of RS-T elevation in acute coronary insufficiency, Irving G. Kroop, Harry L. Jaffe and Arthur M. Master, 465
Simultaneous left- and right-sided intracardiac electrocardiography in man, right bundle branch block, A. Seligmann, M. F. Steinberg, I. G. Kroop, and A. Gresham, 443
Some limitations of vagotomy in the treatment of peptic ulcer, a critical follow-up analysis of fifty cases, Martin J. Healy, Jr. and Paul K. Sauer, 449
Starch sponge, a hemostatic agent, Samuel S. Rosenfeld, 453
Studies with the quantitative cephalin-cholesterol flocculation reaction, Abraham Saifer, 456
Treatment of pernicious anemia with animal protein factor concentrates of bacterial origin, Leo M. Meyer, Norton D. Ritz, Manuel Bowen, George Bock and Julius Rutzky, 464
Use of urinary pigment excretion for the measurement of basal metabolic rate, Jefferson J. Vorzimer, Ira B. Cohen and Jules Joskow, 462
Committee on Public Health Relations, Report of Subcommittee on Proposed Hospital Bond Issue, 743
on Public Health Relations of The New York Academy of Medicine, Report on Hospitalization of veterans, 587
Common cold, Introduction to studies on the, A. R. Dochez, 528
cold, Relationship of bacteria to the, Yale Kneeland, Jr., 534
cold, Research on the, Norman H. Topping, 530
Critique of the present status of the psychotherapies, Robert P. Knight, 100
Crooks, H. M., Jr., Chemistry of chloromycetin, 792

Diagnostic methods, Advances in, Benjamin P. Watson, 747
significance of electrolyte disturbances, John P. Peters, 749
Dillon, Edward S., Discussion on Review of studies on blood sugar, 54
Doan, Charles A., Hypersplenism, 625
Dochez, A. R., Introduction to studies on the common cold, 528
Drugs, Safeguards in the use of new, Austin Smith, 115
Dworin, Milton, Mary Hewitt Loveless and, Allergy and antihistamine therapy, a review, 473

Early ambulation following surgical procedures, James B. Blodgett, 176
Edwin Smith papyrus. See Smith (Edwin) papyrus.
Electric shock therapy, Present status of, Lothar B. Kalinowsky, 541
Electroencephalography, Present status of clinical, Frederic A. Gibbs, 764
Electrolyte disturbances, Diagnostic significance of, John P. Peters, 749
studies in surgical patients, Place of, John S. Lockwood and H. T. Randall, 228
Entomology, Recent advances in medical and veterinary, E. F. Knipling, 388
Evaluation of the surgical treatment of hypertension, R. H. Smithwick, 698
Ewing (James) Memorial Lecture, General view of cancer research, Leonard A. Scheele, 671

Friday Afternoon Lectures
Iron metabolism and hemochromatosis, S. Granick, 403
Modern treatment of syphilis, including syphilis of the central nervous system, Evan W. Thomas, 505
Newer advances in gout, David Adlersberg, 651

Pain in the lumbosacral region, Jefferson Browder, 434
Recent advances in our knowledge concerning the nephrotic syndrome, David Seegal and Arthur R. Wertheim, 605
Therapy of asthma with reference to its psychodynamic pharmacology, Harold A. Abramson, 345
Friends of the Rare Book Room of the Library of The New York Academy of Medicine, Progress report, 194
Furstenberg, A. C., Chronicle of one hundred years of otolaryngology, 775

General view of cancer research, Leonard A. Scheele, 671
Gibbs, Frederic A., Present status of clinical electroencephalography, 764
Goodhart, Robert S., Principles of nutrition therapy, 185
Gout, Newer advances in, David Adlersberg, 651
Graduate Fortnight, 1948
Advances in our knowledge concerning the etiology and treatment of hematological disorders, Cyrus C. Sturgis, 84
Advances in treatment of malignant disease (Ludwig Kast Lecture), C. P. Rhoads, 271
Allergy and antihistamine therapy, a review, Mary Hewitt Loveless and Milton Dworin, 473
Critique of the present status of the psychotherapies, Robert P. Knight, 100
Early ambulation following surgical procedures, James B. Blodgett, 176
Evaluation of the surgical treatment of hypertension, R. H. Smithwick, 698
Management of acute renal failure, I. Snapper, 199
Medical and surgical treatment of peptic ulcer, Chester M. Jones, 488
New analgesic drugs, Henry B. van Dyke, 152
Opening address, Advances in therapy, George Baehr, 3
Principles of nutrition therapy, Robert S. Goodhart, 185
Recent advances in the domain of the anti-histamine substances, phenothiazine derivatives, B. N. Halpern, 323
Recent advances in the therapy of the more common protozoan and helminthic infections of man, Harry Most, 717
Safeguards in the use of new drugs, Austin Smith, 115
Therapeutic role of procaine and its derivatives, E. A. Rovenstine and E. M. Papper, 298
Treatment of Bell's and other palsies, William Bierman, 307
Use of antiepileptic drugs, H. Houston Merritt, 5
Graduate Fortnight, 1949
Address of welcome, advances in diagnostic methods, Benjamin P. Watson, 747
Announcement, 470
Diagnostic significance of electrolyte disturbances, John P. Peters, 749
Present status of clinical encephalography, Frederic A. Gibbs, 764
Granick, S., Iron metabolism and hemachromatosis, 403
Guthrie, Douglas, Rise and progress of medical education in Scotland, 521

Haller, H. L., Chemical aspects of some of the newer insecticides, 374
Halpern, B. N., Recent advances in the domain of the anti-histamine substances, phenothiazine derivatives, 323
Heath, Robert G. and John J. Weber, J. Lawrence Pool, Topectomy, surgical indications and results, 335
Helminthic infections of man, Recent advances in the therapy of the more common protozoan and, Harry Most, 717
Hematological disorders, Advances in our knowledge concerning the etiology and treatment of, Cyrus C. Sturgis, 84
Hemochromatosis, Iron metabolism and, S. Granick, 403
Hitler, Medicine under, George Rosen, 125
Hospital Bond Issue, Subcommittee on Proposed, Report of, 743
Hospitalization of veterans, Report by the Committee on Public Health Relations of The New York Academy of Medicine, 587
Hyperparathyroidism, Results of operations for, William Barclay Parsons, 285

Hypersplenism, Charles A. Doan, 625
Hypertension, Evaluation of surgical treatment of, R. H. Smithwick, 698

In Memoriam. See Obituary.
Insecticides, Chemical aspects of some of the newer, H. L. Haller, 374
Major toxic actions of, Arnold J. Lehman, 382
Introduction to studies on the common cold, A. R. Dochez, 528
Iron metabolism and hemochromatosis, S. Granick, 403

Jones, Chester M., Medical and surgical treatment of peptic ulcer, 488

Kalinowsky, Lothar B., Present status of electric shock therapy, 541
Kast (Ludwig) Lecture, Advances in treatment of malignant disease, C. P. Rhoads, 271
Kneeland, Yale, Jr., Relationship of bacteria to the common cold, 534
Knight, Robert P., Critique of the present status of the psychotherapies, 100
Knipling, E. F., Recent advances in medical and veterinary entomology, 388

Larkey, Sanford V., Thoughts on medical history and libraries—1847 and 1947, 65
Lehman, Arnold J., Major toxic actions of insecticides, 382
Levine, Philip, Rh factor, general significance and methods of study, 244
Libraries, Thoughts on medical history and —1847 and 1947, Sanford V. Larkey, 65
Library notes
Address of acceptance and appreciation of the gift of the Edwin Smith papyrus, George Baehr, 60
Progress report, Friends of the Rare Book Room of the Library of The New York Academy of Medicine, 194
Recent accessions, 61, 130, 264, 331, 397, 537, 601, 666, 795
Liver function tests, Present status of, including observations on the newer flocculation procedures, Maurice Bruger and Elliot Oppenheim, 16
Lockwood, John S. and H. T. Randall, Place of electrolyte studies in surgical patients, 228
Loveless, Mary Hewitt and Milton Dworin, Allergy and antihistamine therapy, a review, 473
Lumbosacral region, Pain in the, Jefferson Browder, 434

Major toxic actions of insecticides, Arnold J. Lehman, 382
Malignant disease, Advances in treatment of, C. P. Rhoads, 271
Management of acute renal failure, I. Snapper, 199
McGavack, Thomas M., Discussion on Review of studies on blood sugar, 56
McGowan, Frank J., Obituary, Eugene Hillhouse Pool—1874-1949, 466
Medical, social and public health aspects of rehabilitation, Howard A. Rusk, 554
education in Scotland, Rise and progress of, Douglas Guthrie, 521
history and libraries—1847 and 1947, Thoughts on, Sanford V. Larkey, 65
and surgical treatment of peptic ulcer, Chester M. Jones, 488
Medicine under Hitler, George Rosen, 125
under Mussolini, Mario Volterra, 364
Medicolegal aspects of the Rh-Hr blood types, Alexander S. Wiener, 255
Merritt, H. Houston, Use of antiepileptic drugs, 5
Microbiology, Section on
Appraisal of the clinical aspects of the Rh factor, Peter Vogel, 261
Chemical aspects of some of the newer insecticides, H. L. Haller, 374
Chemistry of chloromycetin, H. M. Crooks, Jr., 792
Clinical use of chloromycetin in certain bacterial infections, Theodore E. Woodward, 795
Clinical use of synthetic and fermentation chloromycetin, Joseph E. Smadel, 794
Introduction to studies on the common cold, A. R. Dochez, 528
Major toxic actions of insecticides, Arnold J. Lehman, 382
Medicolegal aspects of the Rh-Hr

blood types, Alexander S. Wiener, 255
Recent advances in medical and veterinary entomology, E. F. Knipling, 388
Recent views on the genetics of the Rh-Hr blood factors, Herluf H. Strandskov, 249
Relationship of bacteria to the common cold, Yale Kneeland, Jr., 534
Research on the common cold, Norman H. Topping, 530
Rh factor, general significance and methods of study, Philip Levine, 244
Modern treatment of syphilis, including syphilis of the central nervous system, Evan W. Thomas, 505
Most, Harry, Recent advances in the therapy of the more common protozoan and helminthic infections of man, 717
Movements, Concerning voluntary and involuntary, Abraham M. Rabiner, 566
Mussolini, Medicine under, Mario Volterra, 364

Nephrotic syndrome, Recent advances in our knowledge concerning the, David Seegal and Arthur R. Wertheim, 605
New analgesic drugs, Henry B. van Dyke, 152
New York Academy of Medicine (The), its first hundred years by Philip Van Ingen, a review, Mahlon Ashford, 741
Newer advances in gout, David Adlersberg, 651
Nutrition therapy, Principles of, Robert S. Goodhart, 185

Obituary, Eugene Hillhouse Pool—1874-1949, Frank J. McGowan, 466
Oppenheim, Elliot, Maurice Bruger and, Present status of liver function tests including observations on the newer flocculation procedures, 16
Otolaryngology, Chronicle of one hundred years of, A. C. Furstenberg, 775

Pain in the lumbosacral region, Jefferson Browder, 434
Palsies, Treatment of Bell's and other, William Bierman, 307
Papper, E. M., E. A. Rovenstine and, Therapeutic role of procaine and its derivatives, 298
Papyrus. See Smith (Edwin) papyrus.
Parsons, William Barclay, Results of operations for hyperparathyroidism, 285
Peptic ulcer, Medical and surgical treatment of, Chester M. Jones, 488
Pernicious anemia, Present status of vitamin B_{12} in, Edward H. Reisner, Jr., 429
Peters, John P., Diagnostic significance of electrolyte disturbances, 749
Phenothiazine derivatives, Recent advances in the domain of the anti-histamine substances, B. N. Halpern, 323
Place of electrolyte studies in surgical patients, John S. Lockwood and H. T. Randall, 228
Pool, Eugene Hillhouse—1874-1949, Obituary, Frank J. McGowan, 466
Pool, J. Lawrence, Robert G. Heath and John J. Weber, Topectomy, surgical indications and results, 335
Present status of clinical electroencephalography, Frederic A. Gibbs, 764
status of electric shock therapy, Lothar B. Kalinowsky, 541
status of liver function tests including observations on the newer flocculation procedure, Maurice Bruger and Elliot Oppenheim, 16
status of vitamin B_{12} in pernicious anemia, Edward H. Reisner, Jr., 429
President, Address of the retiring, George Baehr, 145
Presidential address, Benjamin P. Watson, 135
Principles of nutrition therapy, Robert S. Goodhart, 185
Procaine and its derivatives, Therapeutic role of, E. A. Rovenstine and E. M. Papper, 298
Protozoan and helminthic infections of man, Recent advances in the therapy of the more common, Harry Most, 717
Psychiatric perspectives of today, Gregory Zilboorg, 577
Psychotherapies, Critique of the present status of the, Robert P. Knight, 100

Rabiner, Abraham M., Concerning voluntary and involuntary movements, 566

Randall, H. T., John S. Lockwood and, Place of electrolyte studies in surgical patients, 228
Recent advances in the domain of the antihistamine substances, phenothiazine derivatives, B. N. Halpern, 323
advances in our knowledge concerning the nephrotic syndrome, David Seegal and Arthur R. Wertheim, 605
advances in medical and veterinary entomology, E. F. Knipling, 388
advances in the therapy of the more common protozoan and helminthic infections of man, Harry Most, 717
views on the genetics of the Rh-Hr blood factors, Herlaf H. Strandskov, 249
Rehabilitation, Medical, social and public health aspects of, Howard A. Rusk, 554
Reisner, Edward H., Jr., Present status of vitamin B_{12} in pernicious anemia, 429
Relationship of bacteria to the common cold, Yale Kneeland, Jr., 534
Renal failure, Management of acute, I. Snapper, 199
Report of Subcommittee on Proposed Hospital Bond Issue, 743
Research on the common cold, Norman H. Topping, 530
Results of operations for hyperparathyroidism, William Barclay Parsons, 285
Review of studies on blood sugar, Edward Thomas Waters, 32
Discussions, Frederick M. Allen, Edward S. Dillon, Thomas H. McGavack and Charles H. Best, 52
Rh factor, Appraisal of the clinical aspects of the, Peter Vogel, 261
factor, general significance and methods of study, Philip Levine, 244
Rh-Hr blood factors, Recent views on the genetics of the, Herluf H. Strandskov, 249
blood types, Medicolegal aspects of the, Alexander S. Wiener, 255
Rhoads, C. P., Advances in treatment of malignant disease, 271
Rise and progress of medical education in Scotland, Douglas Guthrie, 521
Rosen, George, Medicine under Hitler, 125
Rovenstine, E. A. and E. M. Papper, Therapeutic role of procaine and its derivatives, 298
Rusk, Howard A., Medical, social and public health aspects of rehabilitation, 554

Safeguards in the use of new drugs, Austin Smith, 115
Scheele, Leonard A., General view of cancer research, 671
Scotland, Rise and progress of medical education in, Douglas Guthrie, 521
Seegal, David and Arthur R. Wertheim, Recent advances in our knowledge concerning the nephrotic syndrome, 605
Smadel, Joseph E., Clinical use of synthetic and fermentation chloromycetin, 794
Smith, Austin, Safeguards in the use of new drugs, 115
Smith (Edwin) papyrus, Address of acceptance and appreciation of the gift of the, George Baehr, 60
Smithwick, R. H., Evaluation of the surgical treatment of hypertension, 698
Snapper, I., Management of acute renal failure, 199
Strandskov, Herluf H., Recent views on the genetics of the Rh-Hr blood factors, 249
Sturgis, Cyrus C., Advances in our knowledge concerning the etiology and treatment of hematological disorders, 84
Subcommittee on Proposed Hospital Bond Issue, Report of, 743
Surgical patients, Place of electrolyte studies in, John S. Lockwood and H. T. Randall, 228
procedures, Early ambulation following, James B. Blodgett, 176
treatment of hypertension, Evaluation of, R. H. Smithwick, 698
treatment of peptic ulcer, Medical and, Chester M. Jones, 488
Syphilis, Modern treatment of, including syphilis of the central nervous system, Evan W. Thomas, 505

Therapeutic role of procaine and its derivatives, E. A. Rovenstine and E. M. Papper, 298
Therapy, Advances in, George Baehr, 3
of asthma with reference to its psychodynamic pharmacology, Harold A. Abramson, 345
Thomas, Evan W., Modern treatment of

syphilis, including syphilis of the central nervous system, 505
Thoughts on medical history and libraries—1847 and 1947, Sanford V. Larkey, 65
Topectomy, surgical indications and results, J. Lawrence Pool, Robert G. Heath and John J. Weber, 335
Topping, Norman H., Research on the common cold, 530
Treatment of Bell's and other palsies, William Bierman, 307

Use of antiepileptic drugs, H. Houston Merritt, 5

Van Dyke, Henry B., New analgesic drugs, 152
Van Ingen, Philip, The New York Academy of Medicine, its first hundred years, a review, Mahlon Ashford, 741
Veterans, Hospitalization of, Report by the Committee on Public Health Relations of The New York Academy of Medicine, 587
Vitamin B_{12} in pernicious anemia, Present status of, Edward H. Reisner, Jr., 429
Vogel, Peter, Appraisal of the clinical aspects of the Rh factor, 261
Volterra, Mario, Medicine under Mussolini, 364
Voluntary and involuntary movements, Concerning, Abraham M. Rabiner, 566

Waters, Edward Thomas, Review of studies on blood sugar, 32
Watson, Benjamin P., Address of welcome to 22nd Graduate Fortnight; advances in diagnostic methods, 747
Presidential address, 135
Weber, John J., J. Lawrence Pool, Robert G. Heath and, Topectomy, surgical indications and results, 335
Wertheim, Arthur R., David Seegal and, Recent advances in our knowledge concerning the nephrotic syndrome, 605
Wiener, Alexander S., Medicolegal aspects of the Rh-Hr blood types, 255
Woodward, Theodore E., Clinical use of chloromycetin in certain bacterial infections, 795

Zilboorg, Gregory, Psychiatric perspectives of today, 577